

Template for providing comments on CLH report (Proposal for Harmonised Classification and Labelling)



Effects on human and animal health

General comments			
No.	<u>Column 1</u> Reference to CLH report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations
(1)	General comment on CLH report	<p>Tebuconazole Task Force: we would like to make a general comment on the way the assessment was performed. We have identified certain significant biases within the assessment provided for the CLH classification that we believe warrant attention.</p> <p>These biases are notably severe and are deemed unacceptable, especially when considering the gravity and implications tied to the EU evaluation process.</p> <p>We are of the opinion that a revision is needed to take all the scientific information into consideration in a proper well-balanced weight of evidence</p>	<ul style="list-style-type: none"> - There appears to be a disproportionate emphasis on publications (regardless of their reliability) over standard studies (GLP and OECD), notably evident in the comments concerning toxicity on reproduction and development. - The evaluation and presentation of the validity of protocols used in literature studies are lacking, leading to doubts regarding the validity of included publications and their associated limitations. For transparency reasons the Tebuconazole Task Force indicates in the commenting tables below the Klimisch score for the publications with a score of 3 <i>i.e.</i>, those determined to be unreliable. - The mode of action proposed for ED seems to rely heavily on speculation rather than concrete evidence. - The Klimisch score is presented only for the publications with a score of 3 <i>i.e.</i>, those determined to be unreliable.

Absorption, distribution, metabolism and excretion in mammals			
No.	<u>Column 1</u> Reference to CLH report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations
(1)	<<data point>>, <<description>>	<<MS/EFSA/applicant>>: <<comment>>	

Acute toxicity			
No.	Column 1 Reference to CLH report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(1)	<<data point>>, <<description>>	<<MS/EFSA/applicant>>: <<comment>>	

Short-term toxicity			
No.	Column 1 Reference to CLH report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(1)	8.12 Table 63, page 94, B.6.3.2.2/01 Oral 90-day study in dog Eye toxicity LOAEL	Tebuconazole Task Force: we agree that the NOAEL for the eye toxicity can be established clearly at 1000 ppm (equivalent to 41 mg/kg bw/day) based on the cataractogenic effect observed at the LOAEL of 5000 ppm (equivalent to 212 mg/kg bw/day). Further details regarding the data are given in column 3.	Oral 90-day dog study <i>Vol 3 B.6.3.2.2/01</i> <i>M-028168- 03-1; Guideline in accordance with OECD 409 (1981); GLP compliant</i> Tebuconazole was administered to 4 male and 4 female beagle dogs per dose group at dietary concentrations of 0, 200, 1000, and 5000 ppm for 13 weeks, equivalent to 0, 8.5, 41, and 212 mg/kg bw/day. The eyes of all animals were indirectly examined with Zeiss ophthalmoscopic H instruments before start of study (week -1), and in the third, seventh, tenth and twelfth treatment weeks and in case of the mid and high dose, animals were also examined in the fourteenth week. The eye fundus was photographed by means of a special fundus camera before start of study (week -1) and during the examination in the twelfth week and in the case of the high dose in the tenth and fourteenth weeks in addition. For the ophthalmoscopic examinations the external parts of the eye (conjunctivae, lids, sclera, cornea) were inspected first. The transparent media (cornea, anterior chamber of eye, lens, vitreous body) were appraised, like the eye fundus, by means of ophthalmoscopic instruments. The reported incidences of ophthalmoscopic and histopathological findings are summarized in the table 1 below. The ophthalmoscopic observations are described as lens opacity and lens star as well as other abnormalities in the eye. At the high dose of 5000 ppm, the ophthalmoscopic examination revealed alterations which are attributable to the treatment with tebuconazole, due

Short-term toxicity			
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			<p>to their correlation with dose and their increasing trend during the study. These were lens opacities of varying intensity and varying extent (concentric or stellar). Initially only a few animals were affected (lens opacities were observed for the first time in 2 out of 4 female animals at week 10), but at the end of treatment all the female animals in the highest dose group were affected. The clinical findings ("lens opacity") were the result of morphological degeneration in the area of the anterior wall of the lens or subcapsular cataracta lentis, which was particularly marked in the females. The histological examination of the eyes performed at the end of the study (Week 14) showed (very) slight degeneration of the posterior wall of the lens in animals 641, 645, 647, 715 and 720 in the high dose group of 5000 ppm. Cataract-like eosinophile plaques were found; the normal lens structure had broken down in this area. Animals 648, 650 and 662 in the high dose group (5000 ppm) exhibited clear subcapsular cataracta lentis in both eyes in each case. The lens structure had broken down here both at the posterior and anterior walls, and in particular at the lens equator. Thus, at this high dose of 5000 ppm, the cataract apparition was clearly attributable to the treatment and showed a progressivity with time leading at the end of the study to three female animals out of 4 exhibiting a clear subcapsular cataracta lentis in both eyes. The male dog seems to be less sensitive than the females to the effect on eyes induced by the repeated exposure to tebuconazole. At 5000 ppm in males, the effect on the eye seems to be less advanced. Indeed, the histological examination of the eyes revealed only a (very) slight degeneration of the posterior wall of the lens in all animals at this dose.</p> <p>In the other treated groups (200ppm and 1000 ppm), similar alterations were not detected in both in males and females, neither by the ophthalmoscopic examination during the study nor by the histological examination of the eyes at its end.</p>

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			<p>Therefore, the NOAEL for the eye toxicity can be clearly established at 1000 ppm (equivalent to 41 mg/kg bw/day) based on the cataractogenic effect observed at the <u>LOAEL</u> of 5000 ppm (equivalent to 212 mg/kg bw/day).</p> <p>Table 1: 90-d dog study: incidences of ophthalmoscopic and histopathological findings</p> <table border="1"> <thead> <tr> <th rowspan="2">Dose (ppm)</th> <th rowspan="2">Wk</th> <th colspan="4">Males</th> <th colspan="4">Females</th> </tr> <tr> <th>0</th> <th>200</th> <th>1000</th> <th>5000</th> <th>0</th> <th>200</th> <th>1000</th> <th>5000</th> </tr> </thead> <tbody> <tr> <td colspan="10" style="text-align: center;">Ophthalmoscopic findings</td> </tr> <tr> <td rowspan="5">Lens opacity</td> <td>-1</td> <td>0/4</td> <td>0/4</td> <td>0/4</td> <td>1/4</td> <td>0/4</td> <td>0/4</td> <td>0/4</td> <td>0/4</td> </tr> <tr> <td>7</td> <td>0/4</td> <td>0/4</td> <td>0/4</td> <td>1/4</td> <td>0/4</td> <td>0/4</td> <td>0/4</td> <td>0/4</td> </tr> <tr> <td>10</td> 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<td>2/4</td> </tr> <tr> <td rowspan="5">Fundus slightly unshar p</td> <td>-1</td> <td>0/4</td> <td>0/4</td> <td>0/4</td> <td>0/4</td> <td>0/4</td> <td>0/4</td> <td>0/4</td> <td>0/4</td> </tr> <tr> <td>7</td> <td>-</td> <td>-</td> <td>0/4</td> <td>0/4</td> <td>-</td> <td>-</td> <td>0/4</td> <td>1/4</td> </tr> <tr> <td>10</td> <td>-</td> <td>-</td> <td>0/4</td> <td>2/4</td> <td>-</td> <td>-</td> <td>0/4</td> <td>2/4</td> </tr> <tr> <td>12</td> <td>0/4</td> <td>0/4</td> <td>0/4</td> <td>2/4</td> <td>0/4</td> <td>0/4</td> <td>0/4</td> <td>3/4</td> </tr> <tr> <td>14</td> <td>-</td> <td>-</td> <td>0/4</td> <td>2/4</td> <td>-</td> <td>-</td> <td>0/4</td> <td>3/4</td> </tr> <tr> <td colspan="10" style="text-align: center;">Histopathological findings</td> </tr> <tr> <td colspan="10" style="text-align: center;">Alteration in posterior wall of lens</td> </tr> <tr> <td>Very slight</td> <td>0</td> <td>0</td> <td>0</td> <td>3</td> <td>0</td> <td>0</td> <td>0</td> <td>1</td> <td></td> </tr> <tr> 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(2)	8.12 Table 63, page 94, B.6.3.3.1/01	Tebuconazole Task Force: we are of the opinion that the lens opacities observed at 200 ppm (equivalent to 8 mg/kg bw/day) in two animals	<p>Oral 12-month dog study</p> <p>Vol 3 B.6.3.3.1/01 M-020092- 01-1; Guideline in accordance with OECD 452 (1981); GLP compliant</p>																																																																																																																																																																																																																																																																																																														

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	Oral 12-month dog study Eye toxicity LOAEL	should be considered as incidental. A conservative LOAEL is proposed at the higher dose level of 1000/2000 ppm (equivalent to 47.3 mg/kg bw/day) to consider the possible eye effects caused by a longer exposure. Further details regarding the data are given in column 3 and please see additional explanations in comment (3).	<p>Tebuconazole was administered to four male and four female Beagle dogs via the diet at concentrations of 0, 40, 200 and 1000 ppm (week 1 to 39), 2000 ppm (week 40 to 52) for 12 months. These doses correspond to 0, 1.6, 8 and 47.3¹ mg.kg bw/day. All the animals' eyes were indirectly examined in a darkened room, by Zeiss H (R) ophthalmoscopic instruments, at the times given in the table below. The fundus of the eye was photographed before start of study, and during the final examination, using a special fundus camera. The ophthalmoscopic examinations started with inspection of the external parts of the eye (conjunctivae, lids, sclera, cornea). The transparent media (cornea, anterior chamber of eye, lens, vitreous body) were appraised with the same ophthalmoscopic instruments as the fundus.</p> <p>The reported incidences of ophthalmoscopic findings (lens opacity and lens star) are summarized in the table 2 below.</p> <p>Up to the thirteenth week (first eye examination during the treatment period), no abnormal lens alterations were noted. At the dose of 200 ppm, two female dogs, one from the 26th week (animal P160), and the other from the 32nd week (animal P146) exhibited alterations in the lens. However, from that moment, these alterations were apparent at the same intensity at all the following examination times. In addition, it should be noted that in this dose group, peripheral opacities on lens were already apparent in another animal (animal P172) at the preliminary examination (week -2) suggesting that spontaneous lesions could occur in this dog strain independently of the treatment. This is also supported by the observation of incipient lens starts in animals in other groups (animals P155, P165, P144, P158 in the 40-ppm group and animal P149 in 1000/2000 ppm group) before start of study and which also did not become more pronounced during the study.</p>

¹ calculated:(substance intake /animal / day) /((body weight week -1 + week 52) / 2)

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			<p>At the highest dose tested (1000/2000 ppm), only one female (animal P168) out of 4 exhibited a fine stellar lens opacity which was seen for the first time at week 26 and then only at the following examination time in the 32nd week. All the other animals in this group were either free of lens stars, or the lens stars had already been faintly present at the preliminary examination (animal P149) and did not become more pronounced under the treatment. At the end of the study (52nd week), none of the eight animals (males and females) exhibited ocular effects at the high dose of 1000/2000ppm.</p> <p>The histopathological assessment of the eyes after end of study did not detect any indication of substance-induced alterations.</p> <p>Table 2: 1-y dog study: incidences of ophthalmoscopic findings</p> <table border="1"> <thead> <tr> <th rowspan="2">Dose (ppm)</th> <th rowspan="2">Wk</th> <th colspan="4">Males</th> <th colspan="4">Females</th> </tr> <tr> <th>0</th> <th>40</th> <th>200</th> <th>1000/2000</th> <th>0</th> <th>40</th> <th>200</th> <th>1000/2000</th> </tr> </thead> <tbody> <tr> <td colspan="10">Ophthalmoscopic findings</td> </tr> <tr> <td rowspan="6">Lens opacity</td> <td>-2</td> <td>0/4</td> <td>0/4</td> <td>0/4</td> <td>0/4</td> <td>0/4</td> <td>0/4</td> <td>1/4</td> <td>0/4</td> </tr> <tr> <td>13</td> <td>0/4</td> <td>0/4</td> <td>0/4</td> <td>0/4</td> <td>0/4</td> <td>0/4</td> <td>1/4</td> <td>0/4</td> </tr> <tr> <td>26</td> <td>0/4</td> <td>0/4</td> <td>0/4</td> <td>0/4</td> <td>0/4</td> <td>0/4</td> <td>2/4*</td> <td>1/4</td> </tr> <tr> <td>32</td> <td>0/4</td> <td>0/4</td> <td>0/4</td> <td>0/4</td> <td>0/4</td> <td>0/4</td> <td>2/4*</td> <td>1/4</td> </tr> <tr> <td>39</td> <td>0/4</td> <td>0/4</td> <td>0/4</td> <td>0/4</td> <td>0/4</td> <td>0/4</td> <td>2/4*</td> <td>0/4</td> </tr> <tr> <td>46</td> <td>0/4</td> <td>0/4</td> <td>0/4</td> <td>0/4</td> <td>0/4</td> <td>0/4</td> <td>2/4*</td> <td>0/4</td> </tr> <tr> <td rowspan="6">Lens star</td> <td>-2</td> <td>0/4</td> <td>2/4</td> <td>0/4</td> <td>1/4</td> <td>0/4</td> <td>1/4</td> <td>1/4</td> <td>0/4</td> </tr> <tr> <td>13</td> <td>0/4</td> <td>2/4</td> <td>0/4</td> <td>1/4</td> <td>0/4</td> <td>0/4</td> <td>1/4</td> <td>0/4</td> </tr> <tr> <td>26</td> <td>0/4</td> <td>2/4</td> <td>0/4</td> <td>1/4</td> <td>0/4</td> <td>0/4</td> <td>1/4</td> <td>0/4</td> </tr> <tr> <td>32</td> <td>0/4</td> <td>1/4</td> <td>0/4</td> <td>1/4</td> <td>0/4</td> <td>0/4</td> <td>2/4*</td> <td>0/4</td> </tr> <tr> <td>39</td> <td>0/4</td> <td>1/4</td> <td>0/4</td> <td>1/4</td> <td>0/4</td> <td>0/4</td> <td>2/4*</td> <td>0/4</td> </tr> <tr> <td>46</td> <td>0/4</td> <td>1/4</td> <td>0/4</td> <td>1/4</td> <td>0/4</td> <td>0/4</td> <td>2/4*</td> <td>0/4</td> </tr> <tr> <td>52</td> <td>0/4</td> <td>1/4</td> <td>0/4</td> <td>0/4</td> <td>0/4</td> <td>0/4</td> <td>2/4*</td> <td>0/4</td> </tr> </tbody> </table> <p><i>* Animal P 172 exhibiting lens opacity before the start of the study was not included.</i></p>							Dose (ppm)	Wk	Males				Females				0	40	200	1000/2000	0	40	200	1000/2000	Ophthalmoscopic findings										Lens opacity	-2	0/4	0/4	0/4	0/4	0/4	0/4	1/4	0/4	13	0/4	0/4	0/4	0/4	0/4	0/4	1/4	0/4	26	0/4	0/4	0/4	0/4	0/4	0/4	2/4*	1/4	32	0/4	0/4	0/4	0/4	0/4	0/4	2/4*	1/4	39	0/4	0/4	0/4	0/4	0/4	0/4	2/4*	0/4	46	0/4	0/4	0/4	0/4	0/4	0/4	2/4*	0/4	Lens star	-2	0/4	2/4	0/4	1/4	0/4	1/4	1/4	0/4	13	0/4	2/4	0/4	1/4	0/4	0/4	1/4	0/4	26	0/4	2/4	0/4	1/4	0/4	0/4	1/4	0/4	32	0/4	1/4	0/4	1/4	0/4	0/4	2/4*	0/4	39	0/4	1/4	0/4	1/4	0/4	0/4	2/4*	0/4	46	0/4	1/4	0/4	1/4	0/4	0/4	2/4*	0/4	52	0/4	1/4	0/4	0/4	0/4	0/4	2/4*	0/4
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	32	0/4	0/4	0/4	0/4	0/4	0/4	2/4*	1/4																																																																																																																																																			
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Lens star	-2	0/4	2/4	0/4	1/4	0/4	1/4	1/4	0/4																																																																																																																																																			
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Short-term toxicity			
No.	<u>Column 1</u> Reference to CLH report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations
(3)	8.12 Specific target organ toxicity-repeated exposure - 8.12.2 comparison with the CLP criteria Eyes effects	<p>Tebuconazole Task Force: we are of the opinion that a classification as STOT RE 2 for the eye is not justified based on the available data. Adverse effects in the eyes were observed in two dog studies treated orally with tebuconazole: a 13-week study and a 12-month study. In the 13-week study, progressive ophthalmoscopic alterations (lens opacity) correlated with histological findings (degeneration on the lens) were observed at 212 mg/kg bw/day. This dose is above the guidance value for STOT RE classification. In the one-year dog study, the evidence for eye toxicity is much less and the lens opacities observed after ophthalmoscopic examinations at 200 ppm (equivalent to 8 mg/kg bw/day) in two animals have been considered as incidental. Indeed, these effects observed at 200 ppm (i) did not progress to severe stage, (ii) were not correlated with histopathological findings, (iii) were not dose-related (at the higher dose, only one animal was transitory affected) and (iv) some incipient lens stars were also observed in various animals regardless of the groups concerned before start of study (see column 3 for further explanations).</p> <p>On the other hand, the adversity of the effect exhibited at this dose of 1000/2000 ppm could also be discussed since only one animal was affected and the observed effect was transitory and no correlation with histopathological findings was seen. In addition, in the 13-week dog study,</p>	<p>The eye lesions after an oral repeated exposure of tebuconazole was investigated in rats, mice and dogs. In addition, three 3- to 6- week inhalation studies where eye toxicity was also explored were available in rats, cats and (female) dogs. Ophthalmoscopic and histopathological alterations were observed in dogs after a 90 days and 12 months repeated exposure to tebuconazole whereas no treatment related damage to the eye was found in the other species. The following statement is only focused on the dog studies results.</p> <p><u>Discussion of eye repeated-dose toxicity relevant for classification as STOT RE</u></p> <p>In the 90-day dog study (M-028168- 03-1), the cataract apparition was clearly attributable to the treatment at the highest tested dose of 5000 ppm and showed a progressivity in severity with time, supported by histopathology examinations where morphological degeneration was observed. However, this correlation is much less evident in the one-year dog study (M-020092- 01-1) where doses have been tested up to the to 2000/1000 ppm. Indeed, in the animals where lens opacity was observed after ophthalmoscopic examinations (at 200 ppm and 1000/2000 ppm), these effects did not progress to severe stage, there is no correlation with histopathological findings and no dose response relationship was seen.</p> <p>The fungicidal activity of triazoles is a consequence of their direct inhibition of CYP51 (lanosterol-14-alpha-demethylase). In mammals, CYP51 is part of the pathway leading to the biosynthesis of cholesterol which is the primary sterol in the cell membrane of mammals and is required for sex steroid hormone and vitamin D synthesis. The lens is very susceptible to disturbance of cholesterol biosynthesis pathway since the membranes of the cells of the lens contain high levels of cholesterol. Inhibitors of the cholesterol biosynthesis pathways have been reported to induce cataract in both animals and humans. In the 1-year dog study, the female dog in the highest tested group of 1000/2000 ppm (animal P168) exhibiting alterations in the lens, seems to have a lower individual value</p>

Short-term toxicity							
No.	Column 1 Reference to CLH report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations				
		<p>the administration of the same order of tebuconazole level (1000 ppm equivalent to 41 mg/kg bw/day) caused no effect on eye both in males and females. However, the apparition of the effect due to a longer duration of the same dose exposure cannot be ruled out. Therefore, a conservative LOAEL of 1000/2000 ppm (equivalent to 47.3 mg/kg bw/day) based on the first eye lesions (lens opacity and lens star) seen in one female animal between week 26 and 32 is proposed for the one-year dog study. This dose is also above the guidance value for classification with STOT RE 2 when applying Haber's rule to adjust for the longer duration of the study (Cat. 2 ≤ 25 mg/kg bw/day).</p> <p>Since significant and severe effects on the eyes were detected only above the STOT-RE 2 classification cut-off levels, tebuconazole does NOT meet the criteria for classification for specific target organ toxicity-repeated exposure.</p>	<p>of plasma concentration compared to the controls (Table 4). Moreover, it should be noted that the concentration of plasma cholesterol in this animal P168 (1.55 mmol/l) is below the lower limit of the historical control data (HCD) for this parameter in beagle dogs. In contrast, the two female dogs with lens opacity in the 200ppm group (animals P160 and P146) exhibit individual values of plasma concentration in the same order than the controls of the study and were within the HCD (Table 3). This might suggest that only the eye effects observed in the female exposed at the high dose could be considered treatment-related and the effects observed at the lower dose of 200 ppm should be considered as incidental or as artefacts. Additionally, there are other elements which support that the ocular effects observed at 200ppm should be considered irrelevant:</p> <ul style="list-style-type: none"> (i) these effects do not progress to severe stage, (ii) these effects are not correlated with histopathological findings, (iii) these effects are not dose-related (since at the higher dose, only one animal is transitory affected). In addition, if the observed effects at 200 ppm are considered treatment-related, it is highly questionable whether a 5/10-fold higher dose (1000/2000 ppm) would lead to a lesser response. (iv) some incipient lens stars are also observed in various animals regardless of the groups concerned before start of the one-year dog study (week -2). In the same way, incipient lens stars were also apparent prior the start of the treatment (week -1) in the 90-day dog studies. This suggest that these kind of eye effects may be spontaneous and can appear in absence of treatment. <p>Table 3: 1-y dog study: Plasma cholesterol concentration levels in animal exhibiting lens alterations at the time of the onset of these effects (week 26) and at the end of the study (week 52)</p> <table border="1"> <thead> <tr> <th colspan="2">Plasma cholesterol (mmol/l)</th> </tr> </thead> <tbody> <tr> <td>Female</td> <td>HCD**</td> </tr> </tbody> </table>	Plasma cholesterol (mmol/l)		Female	HCD**
Plasma cholesterol (mmol/l)							
Female	HCD**						

Short-term toxicity									
No.	Column 1 Reference to CLH report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations						
			control	200 ppm		1000/2000			
			Wk	Mean value of 4 animals	Animal P160 (Individual values)	Animal P146 (Individual values)	Animal P168 (Individual values)	lower and upper limit of 2s-range	Age (wk)
			26*	2.53 +/-0.49	4.55	3.47	1.55	2.39-6.09	27-39
			52	4.93 +/-0.67	6.12	5.86	2.65	1.38-6.21	40-52
			<p>* At the dose of 200 ppm, two female dogs (P146), one from the 26th week (P160), and the other from the 32nd week (146) exhibited alterations in the lens. At the highest dose tested (1000/2000 ppm) only one female (P168) out of 4 exhibited a fine stellar lens opacity which was seen for the first time at wk 26 and then only at the following examination time in the 32nd week</p> <p>** Historical Control Data Clinical Chemistry (Beagle Dogs); Statistics 1986 (lower and upper limit of 2s-range)</p> <p>Additionally, it should be noted that the adversity of the effects exhibited at the dose of 1000/2000 ppm could also be discussed. Indeed, only one animal was affected, the observed effects were transitory and no correlation with histopathological findings was seen at this dose. Moreover, in the 90-day dog study, the administration of the same order of tebuconazole level (1000 ppm equivalent to 41 mg/kg bw/day) for 13 weeks caused no effect on eye both in males and females. This is also consistent with the result of a 6-week inhalation study in which female dogs were exposed to up to 914 mg/m³ air of tebuconazole (equivalent to 44 mg/kg bw/day) and where no effects (and notably cataracts) were observed. Nevertheless, the apparition of the effect by a longer duration of the same dose exposure cannot be ruled out. Therefore, a conservative LOAEL of 1000/2000 ppm (equivalent to 47.3 mg/kg bw/day) based on the first eye lesions (lens opacity and lens star) seen in one female animal between week 26 and 32 is proposed for the one-year dog study.</p> <p>In conclusion, adverse effects in the eyes were observed in two dog studies treated orally with tebuconazole. In the 90-day study, progressive ophthalmoscopic alterations (lens opacity) correlated with histological findings (degeneration on the lens) were observed at 212 mg/kg bw/day. This dose is above the guidance value for STOT RE 2 classification. In the</p>						

Short-term toxicity			
No.	<u>Column 1</u> Reference to CLH report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations
			<p>one-year dog study, the evidence for eye toxicity is less. The lens opacities observed after ophthalmoscopic examinations at 8 mg/kg bw/day in two animals have been considered as incidental. However, a conservative LOAEL is proposed at the higher dose level of 47.3 mg/kg bw/day to consider the possible effects caused by a longer exposure. This dose is also above the guidance value for classification with STOT RE 2 when applying Haber's rule to adjust for the longer duration of the study (Cat. 2 ≤ 25 mg/kg bw/day).</p> <p>Since significant and severe effects on the eyes were detected only above the STOT-RE 2 classification cut-off levels, tebuconazole does NOT meet the criteria for classification for specific target organ toxicity-repeated exposure</p>

Genotoxicity			
No.	<u>Column 1</u> Reference to CLH report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations
(1)	<<data point>>, <<description>>	<<MS/EFSA/applicant>>: <<comment>>	

Long-term toxicity and carcinogenicity			
No.	<u>Column 1</u> Reference to CLH report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations
(1)	<<data point>>, <<description>>	<<MS/EFSA/applicant>>: <<comment>>	

Reproductive toxicity			
No.	<u>Column 1</u> Reference to CLH report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations
(1)	8.10.1 Table 47, B.6.6.1.1/01 Effects at the LOAEL. Reproductive.	Tebuconazole Task Force: One dam was found moribund 'possibly due to dystocia' is an inaccurate and speculative conclusion not supported by the study data.	<p>According to the study report, the study pathologist concluded an unknown cause of moribundity with no mention of dystocia. There was no evidence of prolonged gestation in the study either. Furthermore, there was no occurrence of dystocia or prolonged gestation in the two-generation study with two litters (each with 25 rats/sex/dose) from each of two generations.</p> <p>The isolated occurrence of moribundity does not provide evidence of dystocia simply because dead fetuses were present in utero. In fact, the actual time of death could not be established from the raw data.</p> <p>The results of the two-generation study demonstrated clear parental systemic toxicity at the highest dose tested of 1000 ppm (72/97 mg/kg bw/day F0/F1 males, 94/111 mg/kg bw/day F0/F1 females). However, there was no evidence of impaired sexual function or fertility i.e., there was no effect on the time to mating, pregnancy rate, the duration of gestation or on parturition. The body weight of the offspring at birth was reduced at the highest dose tested but pup viability was unaffected. There was no evidence of any adverse effect on the development of the offspring and no observations of malformation.</p>
(2)	8.10.1 Table 47, B.6.6.2.1.2/01 Effects at the LOAEL. Reproductive.	Tebuconazole Task Force: prolonged gestation, two maternal deaths/moribund sacrifices (GD 22 or 23) related to dystocia. This finding was attributed to the severity of the maternal toxicity. There was no evidence of dystocia although this term is used in the study report. Dystocia, by	The variation in mean gestation length was small with mean values being 22.56, 22.63, 22.67, 22.95 days for the control, low, mid and high dose group respectively. It is likely that these mean values fall within normal variation but no historical control data are reported to provide the comparison. As the highest dose caused marked maternal toxicity at the

Reproductive toxicity			
No.	Column 1 Reference to CLH report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
		definition, is a slow or difficult labour or delivery and is typically accompanied by clinical signs of distress in rats i.e., abnormal posture and piloerection.	time of littering, a perturbation of gestation length is a possible consequence related to the impaired pup viability. Both deaths were high dose dams. The deaths are reported as being attributable to dystocia although this conclusion is not supported by the data: One dam was in poor health due to kidney lesions killed GD 23 - not treatment-related. The other dam was found dead GD 22 (the expected day of parturition) having shown no clinical signs to indicate dystocia. The uterus contained two fetuses that appeared normal and four late resorptions. This high dose did impact offspring viability as a consequence of the severity of the maternal toxicity but did not induce dystocia. This conclusion is supported by the two-generation study.
(3)	8.10.1 Table 47, B.6.6.2.1.2/01	Tebuconazole Task Force: Incorrect reference number in multiple places needs resolution Correct reference is B.6.6.2.1.2/02 not B.6.6.2.1.2/01	The study summary does not adequately describe the data and this appears to be the reason why the 'reproductive effects' are over interpreted; the effects have not been aligned with parental toxicity. This is a common theme in this CLH report. The summary is as follows: This non-standard study, describes maternal toxicity (reduced body weight gain of -16%) at the highest dose tested of 60 mg/kg bw/day. Pup viability and body weight were decreased at birth. There was no effect of tebuconazole on the landmarks of development or sexual maturation in the offspring.
(4)	8.10.1 Table 47, B.6.6.3/07 Effects at the LOAEL. Reproductive.	Tebuconazole Task Force: This poor-quality publication (Klimisch 3) concludes prolonged gestation at 50 and 100 mg/kg bw/day based on data from ~ 10 females /dose. The results are inconsistent with properly conducted test guideline studies and other published studies from the same test facility.	Because of problems at parturition, caesarean section was conducted for 2 females on GD 23–25 and the data have been combined with GD 21 data although it is likely the fetuses from the section were dead. The numerical values are consequently distorted and therefore rendered unreliable. The poor quality of this study, inappropriate data handling, highly variable and inconsistent results (inconsistent with other published results from the same test facility – B. 6.6.3/04 /05 & 06) and reporting deficiencies render it unfit for consideration.

Reproductive toxicity			
No.	<u>Column 1</u> Reference to CLH report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations
(5)	8.10.1 Table 47, B.6.6.3/08 Effects at the LOAEL. Reproductive.	Tebuconazole Task Force: Decrease in estradiol in dams (58 %) based on data from 6 pregnant females. These very limited results from a less than adequate published evaluation (Klimisch 3) are not worthy of consideration given the wealth of available meaningful data. The same study reports increased post-implantation loss which is inconsistent with other published studies from the same test facility evaluating the same dose.	There is no indication from the test guideline studies, utilising higher doses, of any impairment of puberty, sexual development or sexual function in support of the claimed result. The publication is unreliable.
(6)	8.10.1 Table 47, page 54, first, second and third text sections	Tebuconazole Task Force: The text describes four other prenatal developmental toxicity studies in rats, rabbits and mice and states that "none of the studies found any adverse effect in preimplantation loss". As dosing commenced on gestation day 6 i.e., post-implantation, no adverse effect of tebuconazole would be expected.	This text should be removed with not being relevant.
(7)	8.10.1 Table 47, B.6.8.3.1.2/01 Pubertal assay Effects at the LOAEL	Tebuconazole Task Force: The text is at variance with the study report and fails to clearly present the results and conclusions. The text should accurately reflect the facts. At 150 mg/kg bw/day, the delay in preputial separation in males and vaginal opening in females was considered a secondary consequence of the marked generalised toxicity.	The absolute weights of several organs (seminal vesicle, dorsolateral prostate, LABC) were decreased in a dose-dependent manner at 75 & 150 mg/kg bw/day. At 150 mg/kg bw/day, atrophic appearance was observed. The effects occurred at doses causing marked effects on body weight/body weight gain indicating that they occurred as a secondary consequence of decreased body weight gain.
(8)	8.10.1 Table 47, B.6.8.3.1.2/02 Late pubertal exposure Effects at the LOAEL	Tebuconazole Task Force: The reliability of the results from this non- GLP, non-guideline study using only 6 male rats is questionable and this	

Reproductive toxicity							
No.	Column 1 Reference to CLH report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations				
		<p>should be made clear. Publication considered Klimisch 3.</p> <p>With the period of exposure being non-standard, from PND 35-56, and with unique endpoints measured in so few animals, the results must not be considered definitive and used only with caution. Inadequate control data i.e., lack of HCD are available to substantiate the claims.</p>					
(9)	8.10.2 page 56 Short summary and overall relevance of the provided information on adverse effects on sexual function and fertility	<p>Tebuconazole Task Force: This text focuses on dystocia and prolonged gestation (which is not evident in the GLP studies) and the effects on the reproductive system of pubertally exposed males (which are reported as secondary to the induced toxicity in a GLP study).</p> <p>The information from repeated dose studies in adult animals, investigating weight and histopathology of reproductive organs is relevant and their omission from this summary is not justified.</p> <p>For 28 & 90 day repeat dose studies, exposure commences in young rats, soon after weaning, making organ weights and histopathology relevant.</p>	<p>The text does not provide an accurate and balanced appraisal of the data. For example, the text refers to observed effects on fertility and sexual function in <u>rabbits and mice</u> although there are no data and, there is undue reliance on the contribution of published data from poor quality or limited studies over and above the comprehensive GLP studies and ignoring those from GLP repeat dose studies.</p> <p>“Indications of endocrine disruption in <u>repeated dose studies</u> and targeted endocrine studies are supportive evidence for the mode of action behind the observed effects” is not only a misleading statement but one that is false.</p> <p>Reference to one publication (Carney, 2004) does not rule out the impact of impaired maternal body weight at the time of parturition which other investigators may report. Neither is it appropriate to conclude on the basis of other azole fungicides. Tebuconazole is the chemical under review in this dossier.</p> <p>The dossier submitter is kindly requested to reconsider their assessment.</p>				
(10)	8.10.3 Page 58 Classification	<p>Tebuconazole Task Force: The dossier submitter conclusion that ‘Classification in Repr. Category 1B for effects on fertility is considered appropriate for classification of tebuconazole, as the CLP criteria are fulfilled by the available information on toxicity of tebuconazole providing clear evidence</p>	<p>This conclusion has been incorrectly reached and the dossier submitter is kindly requested to reconsider their assessment. The outcomes of the relevant studies are summarised below.</p> <table border="1" data-bbox="1187 1321 2072 1364"> <tr> <td></td> <td>B.6.6.1.1/01</td> <td>B.6.6.2.1.2/01</td> <td>B.6.6.2.1.2/02</td> </tr> </table>		B.6.6.1.1/01	B.6.6.2.1.2/01	B.6.6.2.1.2/02
	B.6.6.1.1/01	B.6.6.2.1.2/01	B.6.6.2.1.2/02				

Reproductive toxicity							
No.	Column 1 Reference to CLH report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations				
		of adverse effects that are not considered to be secondary non-specific effects of other toxic effects' is disputed.	Potential adverse effects on sexual function and fertility (ECHA, 2017)	Unpublished. Acceptable.	Unpublished. Acceptable.	Published. Supplementary	
			Alterations to the female and male reproductive system.	No	No	No	
			Adverse effects on onset of puberty.	No direct evaluation. No impairment indicated.	Delayed vaginal opening due to body weight decrement.	Evaluated. No adverse effects observed.	
			Adverse effects on gamete production and transport.	No	Not applicable	No, based on F1 generation	
			Adverse effects on reproductive cycle normality.	No direct evaluation. No impairment indicated.	Not applicable	No, based on F1 generation	
			Adverse effects on sexual behaviour or fertility.	No	Not applicable	No, based on F1 generation	
			Adverse effects on parturition or pregnancy outcomes.	No effect on pregnancy length or on parturition. At birth, reduced pup weight.	Small increase in the duration of gestation. At birth, reduced number of live pups, reduced pup weight. Effects due to severity of maternal toxicity and offspring viability.	No effect on pregnancy length or on parturition. At birth, reduced number of live pups, reduced pup weight. Effects likely due to maternal toxicity although	

Reproductive toxicity							
No.	Column 1 Reference to CLH report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations				
							reported data are very limited.
			Premature reproductive senescence or modifications of other functions dependent on the integrity of the reproductive systems.	No impairment indicated.	No impairment indicated.		No impairment indicated.
(11a)	<p>8.10.3 Page 60 Mode of action analysis</p> <p>AO: Increased gestation length and dystocia KE1: reduced serum estradiol</p>	<p>Tebuconazole Task Force: we disagree with the postulated mode of action showing a relationship between disruptions in steroidogenesis (MIE), reduced serum estradiol levels (KE1) and the adverse outcome: increased gestation length and dystocia (AO).</p> <p>According to the dossier submitter, dystocia and/or prolonged gestation length were seen in three rat studies in one or two animals per dose group. However, we disagree with this conclusion regarding this Adverse Outcome considering that the effects are not supported by the study data and/or are likely attributed to maternal toxicity. See further detail in column 3.</p> <p>In addition, the postulated key event (KE1) "reduced serum estradiol levels" is not sufficiently substantiated. Only one study (prenatal developmental toxicity, B.6.6.3/08) investigated this parameter however this study was non-GLP and non-guideline compliant, Klimisch 3. This study showed a decrease in oestradiol in dams (58 %) exposed at 50 mg/kg bw/day TBZ based on data from 6 pregnant females. These very</p>	<p>We disagree with the conclusion of the dossier submitter regarding dystocia and/or prolonged gestation length seen in three rat studies (2-generation study (B.6.6.1.1/01), DNT study (B.6.6.2.1.2/01) and prenatal developmental toxicity study (B.6.6.3/07)) for the following reasons:</p> <ul style="list-style-type: none"> - In the 2-generation study in rat (B.6.1.1/01), the one dam found moribund 'possibly due to dystocia' is considered a false and speculative conclusion not supported by the study data. Please see further details in comment (1) - In the DNT study in rat (B.6.6.2.1.2/01), the prolonged gestation and the two maternal deaths/moribund sacrifices (GD 22 or 23) is more likely attributed to the severity of the maternal toxicity. Indeed, there was no evidence of dystocia although this term is used in the study report. Dystocia, by definition, is a slow or difficult labour or delivery and is typically accompanied by clinical signs of distress in rats i.e., abnormal posture and piloerection. Please see further details in comment (2) - The published developmental toxicity study (B.6.6.3/07) in which prolonged gestation length was observed is considered of poor quality (Klimisch 3). This non-GLP and non-guideline compliant study are based on data ~ 10 females /dose. Moreover, the results are inconsistent with properly conducted test guideline studies and 				

Reproductive toxicity			
No.	<u>Column 1</u> Reference to CLH report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations
		<p>limited results from a less than adequate published evaluation (low number of exposed dams, high variability, reporting shortcomings) are not worthy of consideration given the wealth of available meaningful data. The same study reports increased post-implantation loss which is inconsistent with other published studies from the same test facility evaluating the same dose. Furthermore, there is no indication from the test guideline studies, utilising higher doses, of any impairment of puberty, sexual development or sexual function in support of the claimed result. The publication is considered unreliable.</p> <p>We are thus of the opinion that this postulated MoA is not applicable since the Adverse Outcome (AO) is considered secondary to severe maternal toxicity or based on conclusions not supported by the study data.</p>	<p>other published studies from the same test facility. Please see further details in comment (4)</p> <p>Please see also comments (9) and (13)</p>
(11b)	8.10.3 Page 60 Mode of action	Tebuconazole Task Force: That the maternal effects are not related to marked systemic toxicity is not supported. The summary tables do not adequately describe the maternal toxicity such that the association with the observed effects has been inadequately assessed. The dossier submitter is kindly requested to reconsider their assessment using the reliable regulatory studies.	
(12)	8.10.3 Page 60 Mode of action analysis	Tebuconazole Task Force: we disagree with the postulated mode of action showing a relationship	Systemic toxicity

Reproductive toxicity			
No.	Column 1 Reference to CLH report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
	AO: Effects on the reproductive system of pubertally exposed male rats	<p>between disruptions in steroidogenesis (MIE), reduced testosterone levels (KE1) and adverse outcomes regarding the reproductive system of pubertal exposed males (AO).</p> <p>Indeed, the conclusion regarding the apical effects on the male reproductive system is based on only one study (i.e., Pubertal development and thyroid function assay in peripubertal male rats (PP male assay) (US EPA TG OPPTS 890.1500), B.6.8.3.1.2/01) where these effects occurred at doses causing marked effects on body weight/body weight gain. According to EPA OPPTS 890.1500 guideline, "<i>abnormal blood chemistry values at termination (particularly creatinine and blood urea nitrogen (BUN)) may indicate that Maximum Tolerated Dose (MTD) is exceeded, even in the absence of a reduction in terminal body weight compared to controls</i>". At 150 mg/kg bw/day, animals showed in addition to decreased body weight gain at termination, lower blood urea concentration (17% reduction, $p \leq 0.01$) and lower creatinine (8% reduction, $p \leq 0.01$), providing additional indications that the Maximum Tolerated Dose (MTD) is likely exceeded. Moreover, the male pubertal assay test guideline states that "<i>a dose level causing more than approximately 6% decrease in body weight gain at termination compared to controls may require additional studies and/or a WoE approach using other information in order to be interpretable.</i>"</p>	<p>At the high dose of 150 mg/kg bw/day TBZ, the mean body weight was statistically significantly reduced by 6 % to 10 % from Day 2 (PND 24) onwards when compared to controls. On Day 2, there was a statistically significant mean body weight loss of 1.5 g ($p \leq 0.01$) compared to a mean body weight gain of 4.9 g in controls. On Day 3 and 4 (PND 25 and 26, respectively) the mean cumulative body weight gain was statistically significantly reduced by 61 % ($p \leq 0.01$) and 33 % ($p \leq 0.01$), respectively, when compared to controls. On Day 8 and 10 (PND 30 and 32, respectively) the mean body weight gain per day was statistically significantly reduced by 30 % ($p \leq 0.01$) and 26 % ($p \leq 0.01$), respectively. Thereafter, the mean cumulative body weight gain remained statistically significantly reduced by 8 % to 28 % throughout the treatment, when compared to controls.</p> <p>At 75 mg/kg bw/day, when compared to controls the mean body weight was statistically significantly reduced by 6 to 7 % on several occasions ($p \leq 0.05$). When compared to controls, the mean body weight gain per day was statistically significantly reduced by 53 % ($p \leq 0.05$) on Day 2 (PND 24). Thereafter, the mean body weight gain per day was comparable to controls except on Day 10 (PND 32, 18% reduction, $p \leq 0.01$) and Day 27 (PND 49, 21 % reduction, $p \leq 0.01$) when compared to controls. The mean cumulative body weight gain was lower than in controls throughout the study, with a statistically significant reduction of between 7% ($p \leq 0.05$) and 19% ($p \leq 0.01$) from Day 3 to 25 (PND 25-47).</p> <p>Overall, there were effects on body weight and body weight gain in males from 75 mg/kg bw/day becoming more severe at 150 mg/kg bw/day (6% and 8% final BWG decreases at 75 and 150 mg/kg bw/day, respectively).</p> <p>Summary Table of body weight gain (BWG) - Individual data</p>

Reproductive toxicity											
No.	Column 1 Reference to CLH report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations								
		<p>For these reasons and in accordance with the OPPTS 890.1500 guideline, we are of the opinion that the effects observed at 150 mg/kg bw/day in this male PP assay must be interpreted with caution since they are likely be secondary to general systemic toxicity. The interpretation should be done together with other studies and the conclusion cannot based only on this study. We are thus of the opinion that this postulated MoA (based on only one study) is not applicable since Adverse Outcomes (AO) are considered secondary to severe systemic toxicity. Moreover, these findings are not supported by data from other studies.</p> <p>Further discussion regarding the general systemic toxicity (e.g., body weight/body weight gains) and the effects on the male reproductive system (delay in preputial separation (PPS), decreased weight of seminal vesicle, dorsolateral prostate, epididymis, LABC and pituitary, macroscopic effects in prostate, seminal vesicle, LABC and testis) is presented in column 3.</p>			Body weight (g)		BWG (g)		BWG		
				Treatment day	PND22	PND23	PND53	Day 2- Day 1	Day 31- Day 1	At Termination (% vs controls)	
				Group	Animal No	Day 1	Day 2	Day 31			
				0 - control	219	66.9	71.6	293	4.7	226.1	
					220	67	71.6	310	4.6	243	
					221	63.9	69.8	301	5.9	237.1	
					222	63.6	69.1	307	5.5	243.4	
					223	63.6	68.8	305	5.2	241.4	
					224	61.2	67	348	5.8	286.8	
					225	58.6	62.1	284	3.5	225.4	
					226	75.1	81.3	331	6.2	255.9	
					227	74.1	79.1	323.6	5	249.5	
					228	74.3	73.1	332.1	-1.2	257.8	
					229	68.4	74.4	302.6	6	234.2	
					230	66.4	70.6	295.6	4.2	229.2	
					231	64.7	69.4	291.5	4.7	226.8	
					232	65.6	72.9	329.7	7.3	264.1	
					233	56.2	61.7	325.3	5.5	269.1	
					MOY	66.0	70.8	312.0	4.9	246.0	
				75 mkd	1249	59	59.7	288	0.7	229	-7%
				1250	66.7	68.3	282	1.6	215.3	-12%	
				1251	63.4	63.7	272	0.3	208.6	-15%	
				1252	65.5	69.7	303	4.2	237.5	-3%	
				1253	61.8	64.7	330	2.9	268.2	9%	

Reproductive toxicity										
No.	Column 1 Reference to CLH report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations							
				1254	63	65.6	284	2.6	221	-10%
				1255	62	63.4	302	1.4	240	-2%
				1256	75.6	77.1	309.3	1.5	233.7	-5%
				1257	72.7	74.7	321.8	2	249.1	1%
				1258	69.9	71.5	307.5	1.6	237.6	-3%
				1259	66.1	68.6	262.8	2.5	196.7	-20%
				1260	67.4	70.9	322	3.5	254.6	4%
				1261	63.2	65.4	280.2	2.2	217	-12%
				1262	62.2	65.9	288.5	3.7	226.3	-8%
				1263	53.9	57.2	285	3.3	231.1	-6%
				MOY	64.8	67.1	295.9	2.3	231.0	-6%
			150 mkd	279	73.1	73	342	-0.1	268.9	9%
				280	69.4	69	323	-0.4	253.6	3%
				281	64.7	62.7	275	-2	210.3	-15%
				282	60.3	60.7	283	0.4	222.7	-9%
				283	61.6	61.9	255	0.3	193.4	-21%
				284	59.4	59.8	262	0.4	202.6	-18%
				285	60.9	60.9	287	0	226.1	-8%
				286	73.4	74	320.4	0.6	247	0%
				287	76.6	77.3	345	0.7	268.4	9%
				288	69.8	68	304.7	-1.8	234.9	-5%
				289	68.8	61.5	268.6	-7.3	199.8	-19%
				290	65.8	58.9	281.2	-6.9	215.4	-12%
				291	62.9	56.1	294.3	-6.8	231.4	-6%

Reproductive toxicity										
No.	Column 1 Reference to CLH report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations							
				292	59.4	59.3	255	-0.1	195.6	-20%
				293	53.6	54.1	273.8	0.5	220.2	-10%
				MOY	65.3	63.8	291.3	-1.5	226.0	-8%
			mkd: mg/kg bw/day The table above clearly indicates that the dose level of 150 mg/kg bw/day significantly resulted in a body weight loss at the beginning of the treatment and in a decrease of over 6% in the mean body weight gain compared to the control group at termination. Individual values exhibited reductions of up to 21% compared to controls. Notably, 9 out of 15 males in the high-dose (HD) group showed a reduction in body weight gain greater than 8%. Considering this marked decrease, alongside the 8% reduction in the mean body weight gain at termination, it is crucial to interpret the results of this study in conjunction with other study data using a weight of evidence approach to ascertain the potential impact of TBZ on the reproductive system of male rats. Slight delay in preputial separation (PPS) in male rats exposed to high dose of TBZ: This apical endpoint (PPS) was investigated in several studies: <ul style="list-style-type: none"> - Study B.6.6.2.1.2/01: Rat developmental neurotoxicity study (GLP) - Study B.6.6.2.1.2/02: Published developmental neurotoxicity study (non-GLP) - Study B.6.6.3/05: Published rat developmental study (non-GLP, Klimisch 3) - Study B.6.8.3.1.2/01: Oral peripubertal study in the rat (GLP) 							
				Study			Exposure		No of animals	Effects on PPS
				Period	Route	Dose levels				

Reproductive toxicity								
No.	Column 1 Reference to CLH report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations					
			B.6.6.2.1.2/01	GD 6 – PND 11	Oral (diet)	HD: 1000 ppm Gestation: 65 mkd Lactation 125.4 mkd	57 – 60 per group	No effect Age at PPS C: 45.4 days HD: 45.7 days
			B.6.6.2.1.2/02	Dams: GD14-PND7 Pups: PND 7-42	Oral (gavage)	HD (dams and pups): 60 mkd	36 - 41 per group	No effect Age at PPS C: 41.2 days HD: 41.2 days
			B.6.6.3/05	GD 7-21 PND 1-16	Oral (gavage)	HD: 50 mkd	Not clearly reported	No effect on PPS
			B.6.8.3.1.2/01	PND 23-53	Oral (gavage)	"LD": 75 mkd HD: 150 mkd	15 per group	Slight delay at 150 mkd Age at PPS C: 40.1 days LD: 41.3 days HD: 42.6 days HCD: 41 (38-44)
<p>LD: low dose; HD; high dose; mkd: mg/kg bw/day; HCD: historical control data; GD: gestation day; PND: post-natal day.</p> <p>Only in one study (B.6.8.3.1.2/01), a mechanistic male peripubertal study, and only at very high dose (150 mg/kg bw/day) with marked effects on body weight, the age at initial preputial separation was statistically significantly increased to PND 42.6 ($p \leq 0.01$) when compared to PND 40.1 in controls. However, this delay is slight when compared to the historical control data (mean value: PND 41) and is within the HCD range (PND 38-44).</p>								

Reproductive toxicity			
No.	<u>Column 1</u> Reference to CLH report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations
			<p>At this dose, a strong decrease of body weight was noted at treatment start (varies from day to day, <i>e.g.</i>, 61% lower bw gain from dosing start to day 4 of dosing). Then, the growth of exposed animals has caught up those of the controls leading to a final body weight difference of 8%. However, this initial growth impairment may have had an impact to the age of PPS initiation since the animals must achieve a certain crucial weight to trigger the onset of puberty. This crucial weight was the same both for the control (199.77 g) and the treated animals (204.68 g), but it takes 2.5 days longer for animal exposed to 150 mg/kg bw/day to achieve this weight and thus to trigger the puberty onset.</p> <p>Therefore, based on the marked body weight effect at 150 mg/kg bw/day at the start and throughout treatment, it can be considered that the slight delay in PPS initiation was due to systemic toxicity. This is supported by the absence of effects on the mean body weight at PPS at both doses.</p> <p>Furthermore, an additional rat developmental toxicity study (B.6.6.3/05) and two developmental neurotoxicity studies (B.6.6.2.1.2/01 and B.6.6.2.1.2/02) showed no effects of tebuconazole treatment given by oral route either by gavage at 50/60 mg/kg bw/day (gavage) or by diet at 1000 ppm (Eq 65-125 mg/kg bw/day) on age at PPS.</p> <p>Effects on male reproductive organ weights and histopathology:</p> <p>In a weight of evidence approach there is no effect on male reproductive organs. A reduction in organ weight and/or histopathological changes indicating small organs for testis, epididymis, prostate, seminal vesicles and LABC for males in a peripubertal assay (B.6.8.3.1.2/01) were seen at high dose levels of 75 mg/kg bw/day and above where evidence of reduced body weight and body weight gain were observed indicating reduced offspring maturity.</p>

Reproductive toxicity			
No.	<u>Column 1</u> Reference to CLH report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations
			<p>The effects observed on the reproductive system of males exposed during puberty were attributed to the decrease in body weight indicating reduced offspring maturity. Additionally, in a comprehensive evaluation, the absence of similar effects in repeat dose studies involving young animals was not taken into consideration by the dossier submitter. Indeed, no effects on male reproductive organs were seen in rats (but also in mice and dogs) in either the regulatory or published repeated dose and reproductive toxicity studies.</p> <p>Furthermore, it's important to note that both male and female animals exposed to tebuconazole throughout their entire lifespans did not exhibit any impairment in their reproductive systems. This was demonstrated through a two-generation study (B.6.6.1.1/01).</p> <p>Please see also comments (9) and (13)</p>
(13)	8.10.3 Page 61 Comparison with the CLP criteria	Tebuconazole Task Force: The conclusions reached by the dossier submitter are disputed as explained in column 3. The dossier submitter is kindly requested to reconsider their assessment.	The conclusion is reached by the dossier submitter based on adverse fertility effects 1) dystocia and prolonged gestation which do not exist in GLP studies, only in unreliable publications and 2) effects on the reproductive system of pubertally exposed males which in fact were attributed to the body weight decrement, and with exclusion of the outcome of repeat dose studies using young animals. Animals exposed throughout their lives to tebuconazole do not have impaired reproductive systems as demonstrated over two generations. The proposed mode of action is not supported.
(14)	8.10.4 Table 50	Tebuconazole Task Force: General comment. The studies are inadequately summarised, and the presentation precludes meaningful understanding of the maternal and developmental findings and their relationship. The dossier submitter is kindly requested to reevaluate the existing, reliable data.	
(15)	8.10.4 rat Table 50 B.6.6.1.1/01	Tebuconazole Task Force: The data are not well summarised. The purpose and strength of a two	For both F0/F1 litters at the highest dose tested, the litter size at birth was lower than controls (↓15%, F1a; ↓26% F1b) suggestive of potential

Reproductive toxicity			
No.	<u>Column 1</u> Reference to CLH report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations
		<p>litter per generation and two generation study is the clear identification of consistent findings. It is therefore important to compare the findings across 4 litters. This approach has not been used and the findings have been presented without context.</p> <p>The conclusion for development is that the body weight of the offspring at birth was reduced at the highest dose tested (in the presence of clear parental systemic toxicity) but pup viability was unaffected.</p> <p>The dossier submitter is kindly requested to reevaluate the existing, reliable data.</p>	<p>pre- or post-implantation loss; this cannot be confirmed or refuted in the absence of uterine examination for implantation scars or from corpora lutea counts. Additionally, the percentage of still born pups was also elevated for the F1a litter but not the F1b litter.</p> <p>A similar response was not seen in the F2 litters born from F1 females treated for much longer than the F0 females i.e., the parents of the F2 litters were exposed to tebuconazole from conception compared to the parents of the F1 litters that were not exposed until post-weaning.</p> <p>There was no effect on pup viability in the neonatal period to day 5 or thereafter to weaning in either generation.</p> <p>There was no evidence of any adverse effect on the development of the offspring and no observations of malformation</p>
(16)	8.10.4 rat Table 50 B.6.6.2.1.1/01	<p>Tebuconazole Task Force: This study is acceptable only as supplementary data because of significant deviations from the test guideline: no food intake data; body weights not at 3 day intervals pre/post dosing; <50% fetuses examined for visceral anomalies; pre/post implantation loss not reported; other reporting deficiencies including no individual fetal data. The deficiencies appear to not to have been considered.</p> <p>The data are inadequately summarised. The dossier submitter is kindly requested to reevaluate the summary.</p>	<p>The study results are more accurately presented as follows:</p> <p>Maternal effects</p> <p>100 mg/kg bw/day: Initial body weight loss days 6-11, ↓ body weight gain for dosing period (-74 %), ↑ clinical signs (light/hard faeces & ↑ urination)</p> <p>LOAEL 30 mg/kg bw/day: ↓ weight gain for dosing period (-16%)</p> <p>NOAEL 10 mg/kg bw/day</p> <p>Developmental effects</p> <p>LOAEL 100 mg/kg bw/day</p> <p>↓ fetal body weight (-11%), ↑ mean number late resorptions (2.3 cf. 1.4 controls) but no ↓ in number live fetuses (7.3 cf. 7.9 control), ↑ fetal & litter incidence of malformations (6.9%/37.5% cf. 1.7%/13.6% controls).</p> <p>NOAEL 30 mg/kg bw/day</p> <p>The malformations related to the eyes and were not seen in any other study in the rat performed at other test facilities using a different rat strain or, at higher dose levels. Furthermore, the eye malformations were</p>

Reproductive toxicity			
No.	Column 1 Reference to CLH report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
			found to be specific to the breeding colony used to provide the test animals.
(17)	8.10.4 rat Table 50 B.6.6.2.1.1/02	Tebuconazole Task Force: This is an acceptable and reliable study. The only TG deviation was food intake data not collected at 3-day intervals. The data are inadequately summarised. The dossier submitter is kindly requested to reevaluate the summary.	The study results are more accurately presented as follows: Maternal effects 120 mg/kg bw/day: Initial body weight loss days 6-10, ↓ body weight gain for dosing period (-29%), ↓ food intake for dosing period (-15%), ↑ relative liver weight (+15%). LOAEL 60 mg/kg bw/day: ↓ body weight gain for dosing period (-15%), ↓ food intake for dosing period (-7%), ↑ relative liver weight (8%) NOAEL 30 mg/kg bw/day Developmental effects LOAEL 120 mg/kg bw/day: ↓ fetal body weight (-11%), ↑ post-implantation loss (22.1% cf. 4.6% controls) hence ↓ number live fetuses (9.7 cf. 12.0 controls), ↑ fetal & litter incidence of skeletal variations relating to supernumerary ribs and retarded ossification as a consequence of impaired growth. Two fetuses with malformation within HCD for fetal & litter incidence. NOAEL 60 mg/kg bw/day
(18)	8.10.4 rat Table 50 B.6.6.2.1.1/03	Tebuconazole Task Force: Although an investigative maternal toxicity study, some developmental data (collected on gestation day 16) are available and worthy of note. The magnitude of the maternal effect for these studies in pregnant rats should not be ignored or underestimated as they appear to have been. The dossier submitter is kindly requested to reevaluate the summary.	Maternal effects 120 mg/kg bw/day: Initial body weight loss days 6-11, ↓ body weight gain for dosing period (-60%), ↓ food intake days 6-9 (-41%), ↓ water intake, ↑ clinical signs (light/hard faeces, piloerection, ↑ urination), ↑ relative liver weight (13%), liver histopathology – hyperplasia of bile duct, ↑ glycogen content, periportal inflammation and pigmentation, adrenal histopathology - cytoplasmic vacuolation of zona fasciculata and vacuolation of zona glomerulosa. Developmental effects

Reproductive toxicity			
No.	<u>Column 1</u> Reference to CLH report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations
			120 mg/kg bw/day: ↓ fetal body weight (-13%), ↑ post-implantation loss (21.8% cf. 6.0% controls) hence ↓ number live fetuses (9.5 cf. 11.1 controls).
(19)	8.10.4 rat Table 50 B.6.6.2.1.2/01	Tebuconazole Task Force: The data are inadequately summarised and fail to acknowledge the extent of the maternal toxicity induced. This omission does not allow for the developmental effects to be put in context. The dossier submitter is kindly requested to reevaluate the summary.	Maternal effects LOAEL 1000 ppm (65/125 mg/kg bw/day gestation/lactation): ↓ body weight gain GD 6-21 (-22%) and LD 1-7 (-82%), ↓ feed consumption GD 6-21 (-14%) and LD 1-12 (-18%). NOAEL 300 ppm (22/41 mg/kg bw/day gestation/lactation) Developmental effects LOAEL 1000 ppm (65/125 mg/kg bw/day gestation/lactation): ↓ mean number live born (13.1 cf. 13.9 controls), ↑ still born (7 cf. 2 controls), ↑ neonatal deaths (22 cf. 4 controls), ↓ viability index LD5 (91.7% cf. 97.9% controls), ↓ body weight LD5 (-15%) LD 22 (-22%) Selected F1 ↓ body weight day 5 (males -13%, females -15%), ↓ body weight gain – males days 5-86 (-8%), females days 5-58 (-6%), delayed vaginal opening (33.2 days cf. 31.6 days control due to ↓ body weight (-12%). NOAEL 300 ppm (22/41 mg/kg bw/day gestation)
(20)	8.10.4 rat Table 50 B.6.6.2.1.2/02	Tebuconazole Task Force: The published study is acceptable as supplementary data for maternal and developmental effects only. The neuropathological findings were withdrawn as artefacts by the authors. The results for development are inadequately presented. The dossier submitter is kindly requested to reevaluate the summary.	Maternal effects 60 mg/kg bw/day: ↓ body weight gain (-16%) Developmental effects 60 mg/kg bw/day: Post-natal day 0: ↓ number live pups (9.7 cf. 11.2 controls), ↑ number dead pups (2.2 cf. 0.4 controls), ↓ pup body weight (-13%). No effect on developmental landmarks or sexual maturation. ↑ relative liver weight (F1 males 10%, F1 females 12%) postnatal day 46
(21)	8.10.4 rat Table 50 B.6.6.2.1.3/01	Tebuconazole Task Force: This study is acceptable only as supplementary data because of significant deviations from the test guideline: food	

Reproductive toxicity			
No.	Column 1 Reference to CLH report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
		<p>consumption and body weights not at 3 day intervals; <50% fetuses examined for visceral anomalies; pre/post implantation loss not reported; other reporting deficiencies including no individual fetal data.</p> <p>The deficiencies have not been acknowledged but the Task Force agrees that the conclusions are correct.</p>	
(22)	8.10.4 rat Table 50 B.6.6.3/07	<p>Tebuconazole Task Force: This poor-quality publication (Klimisch 3) provides only unreliable results based on small numbers of animals. The results are highly variable and inconsistent with other publications from the same group. There are notable reporting deficiencies.</p> <p>Because of problems with parturition, caesarean section was conducted for 2 females on GD 23–25 and combined with GD 21 data. The numerical values are distorted by this and rendered unreliable.</p> <p>This study has no credible value in the overall assessment.</p>	<p>The results are more accurately summarised as follows.</p> <p>100 mg/kg/day: ↓ maternal weight gain GD 7-21 (-29%), ↑ gestational length causing loss of fetuses & postnatal death of pups, ↓ fetal weight GD 21 (due to high control values) but no ↓ birth weight, ↑ AGD in females GD 21 & PND 1 but values inconsistent (inconsistent results at 50 mg/kg bw/day also with no effect on AGD according to B.6.6.3/08). No effects on onset of puberty and mating behaviour up to 50 mg/kg bw/day cited in other publications from this research group (B.6.6.3/05; B.6.6.3/06). Reported effects on AGD are either not treatment-related or of no toxicological significance.</p> <p>Nipple retention in males PND 13 at both dose levels (3.43 and 3.07 areolae at 50 and 100 mg/kg bw/day vs 2.08 areolae in controls) with no clear dose-response. No effect on mammary gland development in male pups at PND 22 and PND 50 (B.6.6.3/05) from the same research group.</p> <p>50 mg/kg/day should be described as NOAEL</p>
(23)	8.10.4 rat Table 50 B.6.6.3/08	<p>Tebuconazole Task Force: Another publication of poor quality that should be considered unreliable (Klimisch 3) with conclusions based on small number of animals, highly variable results and notable reporting deficiencies.</p>	<p>Cited results (derived from 9 females and only 6 in controls), are ↑ post-implantation loss, ↓ maternal estradiol. No effect on AGD at 50 mg/kg/day.</p> <p>This study is not sufficiently robust to provide any meaningful data for inclusion in the overall assessment.</p>

Reproductive toxicity			
No.	Column 1 Reference to CLH report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
		Speculative reference to possible indicator of demasculinization of male foetuses is not supported by the Task Force.	
(24)	8.10.4 rat Table 50 B.6.6.3/04, B.6.6.3/05, B.6.6.3/06	<p>Tebuconazole Task Force: Three publications from one flawed study (Klimisch 3) designed to evaluate mixtures of pesticides. The results are unreliable as based on too few animals, inconsistent results between publications from the same group, and notable reporting deficiencies.</p> <p>Lack of maternal toxicity at 50 mg/kg/day is inconsistent with other studies.</p> <p>These studies are not sufficiently robust to provide any meaningful data for inclusion in the overall assessment. The dossier submitter is kindly requested to reevaluate the contribution of these studies.</p>	<p>B.6.6.3/04. Claims tebuconazole affected steroidogenesis in vitro causing inhibition of the androgen receptor and reducing the action of T3. Unlikely that multiple targets are affected and more likely unspecific responses. Result not consistent with those of other studies i.e. no maternal toxicity as seen in other studies.</p> <p>↑ AGD females PND1 ≥ 15 mg/kg bw/day (but no dose-response), ↑ nipple retention males PND13 50 mg/kg bw/day. No effect on AGD at same dose (B.6.6.3/08 with longer dosing period).</p> <p>B.6.6.3/05. 50 mg/kg/day: No effect on puberty onset, reproductive organs (including sperm analysis), thyroid, mammary gland development in males and females at PND 22 and PND 50. No evidence of developmental neurotoxicity (behavioural, motor activity, learning & memory), mating behaviour or sex hormones in offspring.</p> <p>B.6.6.3/06. 50 mg/kg/day. No effect on puberty onset (balano-preputial separation/ vaginal opening), oestrus cyclicity, postnatal development, reproductive organs or levels of kisspeptin (a positive regulator of the hypothalamic–pituitary–gonadal axis, which plays a key role in the initiation of puberty) mRNA in the hypothalamus (PND 50).</p>
(25)	8.10.4 rabbit Table 50 B.6.6.2.2.1/01	<p>Tebuconazole Task Force: This study is acceptable only as supplementary data because of significant deviations from the test guideline: <16 pregnant dams/dose, no food intake data; body weights not at 3 day intervals; pre/post implantation loss not reported; other reporting deficiencies including no individual fetal data.</p> <p>The deficiencies appear have not been acknowledged. The results are less than</p>	<p>The results are more accurately summarised as follows.</p> <p>Maternal effects NOAEL 30 mg/kg bw/day [↓ weight gain for dosing period (-26%) disregarded on basis of weight of evidence from other, acceptable studies.]</p> <p>Developmental effects NOAEL 30 mg/kg bw/day</p>

Reproductive toxicity			
No.	Column 1 Reference to CLH report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
		adequately presented. The dossier submitter is kindly requested to reevaluate the summary.	[Non-significant ↑ post-implantation loss with no corresponding ↓ number live fetuses, therefore an incidental finding.]
(26)	8.10.4 rabbit Table 50 B.6.6.2.2.1/02	Tebuconazole Task Force: This is an acceptable study with minor deviations from the test guideline (<16 pregnant dams/dose; food intake not at 3-day intervals. The results are adequately presented if devoid of detail.	The results are more accurately summarised as follows. Maternal effects LOAEL 100 mg/kg bw/day: Initial body weight loss days 6-9, ↓ body weight gain for dosing period (-38%), ↓ food intake for dosing period (-12%). NOAEL 30 mg/kg bw/day Developmental effects LOAEL 100 mg/kg bw/day: ↑ post-implantation loss 27.4% cf. 8.3% controls, hence ↓ number live fetuses (6.4 cf. 7.4 controls), ↓ fetal weight (-6%), ↑ fetal anomalies NOAEL 30 mg/kg bw/day
(27)	8.10.4 rabbit Table 50 B.6.6.2.2.1/03	Tebuconazole Task Force: This is an acceptable study with minor deviations from the test guideline. However, it really should be clarified that this was a follow up study with an additional phase for clinical chemistry, organ weights & liver histopathology. It is noted that the clustering of malformation has not been considered and so the information has been included in column 3.	The results are more accurately summarised as follows. Maternal effects LOAEL 100 mg/kg bw/day: Initial body weight loss days 6-15, ↓ body weight gain for dosing period (-59%), ↓ food intake days 6-11 (-29%), days 11-15 (-10%) and overall dosing period days 6-19 (-17%) NOAEL 30 mg/kg bw/day [Single cell necrosis in the liver was observed in all tebuconazole treated animals (5/group). Focal liver necrosis observed in one animal only, 30 mg/kg bw/day, and none at 100 mg/kg bw/day. Findings questionable as indicative of maternal toxicity.] Developmental effects LOAEL 100 mg/kg bw/day: ↓ fetal weight (-7%), ↑ fetal anomalies [Marginal, non-significant ↑ post-implantation loss with no ↓ number live fetuses therefore an incidental finding.] NOAEL 30 mg/kg bw/day

Reproductive toxicity			
No.	<u>Column 1</u> Reference to CLH report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations
			<p>[↑ fetal anomalies but dissimilar to those at 100 mg/kg bw/day and therefore an incidental finding.]</p> <p>B.6.6.2.2.1/02 & B.6.6.2.2.1/03 were conducted using the Chinchilla rabbit and >10 years apart. The type and incidence of malformation was not consistent for both studies; no external malformation was observed at 30 mg/kg bw/day in the first study although 3 were found in the second study. Historical control data were obtained for the period 1989-1995 (M-276159-01-1) which indicated that a clustering of malformation occurred around 1992. The clustering was not only caused by the higher rate of affected studies but also by the higher incidence of external malformations within a given study.</p> <p>The most likely explanation for this transient clustering, resulting in high biological variability of observed external malformations in 1992, is colony management at the breeder with a likely peak of genetically pre-disposed animals. The observation in the studies that those fetuses affected had multiple malformations is more indicative of congenital defects prevalent in the colony than chemically induced malformation which would be more consistent in type and reproducible across studies.</p> <p>The evidence for an association between tebuconazole and fetal malformation in the rabbit is not convincing. Neither the type nor incidence of malformation are reproducible across studies or consistent with dose in the same strain of rabbit. No malformation was noted in the Himalayan rabbit study providing supplementary data. The historical data clearly show that the most likely cause of the malformation in the Chinchilla rabbit is due to colony management at the breeder. The developmental NOAEL is therefore considered to be 30 mg/kg bw/day based on impaired fetal growth (lower fetal body weight) and fetal viability (increased post-implantation loss) occurring in the presence of maternal toxicity at 100 mg/kg bw/day.</p>
(28)	8.10.4 rabbit Table 50 B.6.6.2.2.1/04	Tebuconazole Task Force: This study was not comparable with OECD TG 414 (1981) as	The results are more accurately summarised as follows. Maternal effects

Reproductive toxicity			
No.	Column 1 Reference to CLH report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
		<p>reported, having only one test group and terminating on GD 19. Neither was it fully GLP. The study was conducted for organ weight determination, histopathology of liver, ovaries, adrenals and placentas, liver and adrenal enzyme activities, adrenal steroid measurements, maternal plasma and fetal tissue tebuconazole concentrations and so providing acceptable supplementary data.</p>	<p>100 mg/kg bw/day: Initial weight loss with day 6 weight not regained, ↓ body weight gain days 6-19 (-181%), ↓ food intake (days 6-9 -43%), adrenal hypertrophy zona fasciculata, ↑ adrenal 11β-hydroxylase activity and 11-deoxycorticosterone in mitochondria, ↑ adrenal 11-deoxycorticosterone.</p> <p>Developmental effects 100 mg/kg bw/day: ↓ fetal weight (-12%)</p>
(29)	8.10.4 mouse General comment	<p>Tebuconazole Task Force: The NMRI strain of mouse is of questionable suitability for use in prenatal developmental toxicity studies because of the high incidence of spontaneous malformation including cleft palate, exencephaly, open eye amongst others.</p> <p>The collated data from all studies, including the dermal study, demonstrate the prevalence of malformation in this strain and the commonality of malformation across studies.</p> <p>Whilst elevation of the total incidence of malformation may be observed at the highest doses of tebuconazole in the oral gavage and dermal developmental toxicity studies, across study consideration of the specific malformations does not provide evidence of any consistent increase with dose. The malformations are mostly common to all doses. For this reason, the evidence for tebuconazole causing malformation in the mouse is equivocal. The Dossier submitter is kindly requested to take this into account in their assessment.</p>	<p>The suitability of the NMRI mouse has been questioned in publications by ██████ (M-248213-01-1), ██████ (M-066928-01-1), ██████ (M-034685-01-1), ██████ (M-034671-02-1) and others.</p> <p>Additionally, at the time of the study conduct, the NMRI strain of mouse was possibly an inbred strain and therefore unsuitable for use to assess developmental effects due to high spontaneous rate of malformation.</p> <ul style="list-style-type: none"> • <u>INBRED STRAINS OF MICE, Updated 9 Apr. 1998, ██████ ██████, MRC Toxicology Unit, Hodgkin Building, University of Leicester, UK.</u> <p><u>NMRI Mice: Inbr: F50 (Lac). Albino. Genetic. Origin: Non-inbred Swiss mice from ██████ to ██████ 1937. Inbred by ██████ known as NIH/PI. To US Naval Med. Res. Inst. at F51, known as NMRI (but not histocompatible on arrival at Laboratory Animals Centre). NOTE: Many colonies of NMRI, particularly European, are random or pen-bred.</u></p> <ul style="list-style-type: none"> • Charles River https://www.criver.com/products-services/find-model/nmri-mouse?region=3671

Reproductive toxicity			
No.	<u>Column 1</u> Reference to CLH report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations
			<p>NMRI Mice: Nomenclature Crl:NMRI(Han) (outbred)</p> <p>Strain origin: Swiss-type mouse given by ██████████ to ██████████ in 1937. He maintained an inbred line of these animals for 51 generations, before animals were transferred to the Naval Medical Research Institute. Introduced into Charles River in 1979 from the Central Institute for Laboratory Animal Breeding Hannover (Germany).</p> <ul style="list-style-type: none"> • <u>JMPR Review Tebuconazole 2010, page 539</u> <p>Suitability of mice for developmental toxicity study</p> <p>The expert opinion of ██████████ (2005) contains a discussion of the evolution of the current teratology guidelines and a history of the use of mice in regulatory toxicology studies. ██████████ (2005) suggested that NMRI mice are not a suitable model for the evaluation of teratogenic effects because of lack of an adequate historical control database, high incidence of spontaneous malformations (cleft palate), high rate of spontaneous genetic defects and high reactivity to environmental stress. ██████████ (2005) concluded that "observations of malformations in the fetuses of NMRI mice should not be considered an appropriate criterion for calculation of a NOEL [no-observed-effect level]."</p> <p>All studies of tebuconazole were conducted using this strain of mouse. The collated data from all studies, including the dermal study, demonstrate the prevalence of malformation in this strain and the commonality of malformation across studies (See Table below). Whilst elevation of the total incidence of malformation may be observed at the highest doses of tebuconazole in the oral gavage and dermal</p>

Reproductive toxicity			
No.	<u>Column 1</u> Reference to CLH report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations
			<p>developmental toxicity studies, across study consideration of the specific malformations does not provide evidence of any consistent increase with dose. The malformations are mostly common to all doses. For this reason, the evidence for tebuconazole causing malformation in the mouse is equivocal.</p> <p>As the NMRI strain of mouse is particularly unsuitable for use in prenatal developmental toxicity studies, classification of tebuconazole, or indeed any other chemical as a developmental toxicant should not be based on the fetal data from studies conducted using this strain.</p> <p>Table: Interstudy comparison of external fetal malformation in the NMRI Mouse (% fetuses (% litters) affected)</p>

Endpoint	Dose Level of Tebuconazole (mg/kg/day)														
	0 ¹	0 ²	0 ²	0 ³	1 ²	3 ²	10 ¹	10 ²	30 ₁	30 ²	100 ¹	100 ²	100 ³	300 ³	100 ₀ ³
No. of fetuses (litters) evaluated	236 (24)	31 (29)	21 (21)	301 (25)	239 (20)	186 (18)	23 (22)	321 (28)	23 (2)	27 (24)	202 (20)	211 (26)	332 (25)	337 (24)	285 (25)
No. of fetuses (litters) with findings	1 (1)	1 (1)	1 (1)	9 (8)	4 (4)	3 (3)	4 (2)	4 (3)	0 (0)	4 (1)	13 (8)	22 (12)	10 (8)	6 (6)	15 (9)
Exencephaly	-	-	-	0.3 (4.0)	-	-	-	0.9 (10.7)	-	0.7 (4.2)	-	5.7 (19.2)	0.3 (4.0)	-	0.7 (4.0)
Open eye	-	-	-	-	-	-	-	0.6 (7.1)	-	0.6 (3.6)	-	3.3 (11.5)	-	-	-
Cleft palate	0.4 ^a (4.2 ^a)	0.7 (3.5)	-	2.7 (28.0)	1.3 (15.0)	0.5 (5.6)	1.7 (8.7)	0.3 (3.6)	-	0.7 (4.2)	3.0 (20.0)	4.7 (26.9)	2.4 (28.0)	1.2 (16.7)	4.2 (28.0)
Small upper jaw	0.4 ^a (4.2 ^a)	-	-	-	-	-	0.4 (4.6)	-	-	-	0.5 (5.0)	-	-	-	-
Malrotated/malposition hindlimb	-	-	0.5 (4.8)	0.3 (4.0)	-	-	-	-	-	-	-	-	0.3 (4.0)	0.3 (4.2)	0.7 (8.0)
Abnormal tail	0.4 ^a (4.2 ^a)	-	-	0.3 (4.0)	0.4 (5.0)	1.1 (11.1)	-	0.3 (3.4)	-	-	0.5 (5.0)	1.0 (7.7)	-	0.3 (4.2)	-
Multiple malformation	0.4 ^a (4.2 ^a)	-	-	-	-	-	-	-	-	-	-	-	-	-	-

¹ M-019841-02-1 ² M-019174-02-1 ³ M-019253-01-1
^a Multiple malformation: cleft face/jaw/palate, dysplasia of extremities, deformed spine and ribs, shortened tail

Reproductive toxicity			
No.	<u>Column 1</u> Reference to CLH report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations
(30)	8.10.4 mouse Table 50 B.6.6.2.3.1/01	<p>Tebuconazole Task Force: This study is acceptable only as supplementary data because of significant deviations from the test guideline: no food intake data; <50% fetuses examined for visceral anomalies; pre/post implantation loss not reported; reporting deficiencies.</p> <p>The deficiencies have not been acknowledged. The results are inadequately presented.</p> <p>The NMRI strain of mouse has been used which is known to be unsuitable for use in this study type due to the high rates of spontaneous malformation. The Dossier submitter is kindly requested to take this into account in their assessment.</p>	<p>The results are more accurately summarised as follows.</p> <p>Maternal effects: NOAEL 100 mg/kg bw/day</p> <p>Developmental effects</p> <p>LOAEL 100 mg/kg bw/day: ↑ incidence of malformation - 13 fetuses in 8 litters cf. single incidence in controls. Malformation primarily cleft palate, a common observation in mice.</p> <p>Reported increase in runts but with no significant decrease in fetal weight (-4%) therefore disregarded.</p> <p>[A reported increase in placental weights of 0.01g is not of biological or toxicological relevance and therefore disregarded.]</p> <p>NOAEL 30 mg/kg bw/day.</p> <p>The maternal body weight effect is not consistent with the supplementary phase of the study nor with the acceptable study B.6.6.2.3.1/03.</p>
(31)	8.10.4 mouse Table 50 B.6.6.2.3.1/02	<p>Tebuconazole Task Force: It should be explained that this is non-guideline supplementary study to B.6.6.2.3.1/01, to investigate maternal toxicity – non-standard endpoints using 10 mice/dose. No fetal examination. It is not an OECD 414 study as indicated.</p> <p>It should also be noted that the results for maternal body weight gain are not consistent between the main and supplementary phases of this study because this impacts study reliability.</p> <p>It is noted that there is a reported comment as follows: LOAEL / NOAEL Not reliable for setting NOAEL (small group size). The group size of 10 is more than in some of the publications whose</p>	<p>Maternal effects</p> <p>100 mg/kg bw/day: ↓ body weight gain days 6-15 (-32%), ↑ liver triglyceride (+164%), ↑ relative liver weight (27%), ↑ liver fat content, ↑ liver vacuolation</p> <p>30 mg/kg bw/day: No effect on body weight gain days 6-15 (28%), ↑ relative liver weight (12%), ↑ liver fat content</p> <p>LOAEL 20 mg/kg bw/day: ↓ body weight gain days 6-15 (-26%), ↑ relative liver weight (15%), ↑ liver fat content</p> <p>NOAEL 10 mg/kg bw/day</p> <p>Section states LOAEL Not reliable for setting NOAEL (small group size) and also Effects at the LOAEL, maternal toxicity?</p> <p>This statement cannot be understood. No dose is defined as being the LOAEL.</p>

Reproductive toxicity			
No.	Column 1 Reference to CLH report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
		results seem to be deemed relevant to defining toxicity endpoints.	
(32)	8.10.4 mouse Table 50 B.6.6.2.3.1/03	Tebuconazole Task Force: Acceptable study with supplementary phase investigating maternal toxicity using non-standard endpoints. The NMRI strain of mouse has been used which is known to be unsuitable for use in this study type due to the high rates of spontaneous malformation. The Dossier submitter is kindly requested to take this into account in their assessment.	The results are more accurately summarised as follows. Maternal effects LOAEL 100 mg/kg bw/day: ↓ body weight gain days 6-16 (-13%), ↓ food consumption days 6-16 (-4%), ↑ relative liver weight (20%), ↑ lipid storage, clinical chemistry and histopathology, ↑ reticulocytes, ↑ spleen weight (45%) NOAEL 30 mg/kg bw/day [↑ liver enzyme induction, lipid storage & liver vacuolization considered adaptive] Developmental effects LOAEL 100 mg/kg bw/day: ↑ post-implantation loss (35.3% cf. 8.4% controls) hence ↓ number live fetuses (8.1 cf. 10.9 controls), [↓ fetal weight (-8%) and not clearly treatment-related], ↑ malformation (litter incidence 46% cf. 3.5% controls) including exencephaly, cleft palate, open eyes, vertebral bodies/arches missing/dysplastic. NOAEL 30 mg/kg bw/day [Non-significant ↑ post-implantation loss (12.5% cf. 8.4% controls) with no ↓ number live fetuses therefore an incidental finding.]
(33)	8.10.4 mouse Table 50 B.6.6.2.3.2/01	Tebuconazole Task Force: Acceptable study with supplementary phase investigating maternal toxicity using non-standard endpoints. The NMRI strain of mouse has been used which is known to be unsuitable for use in this study type due to the high rates of spontaneous malformation. The Dossier submitter is kindly requested to take this into account in their assessment.	The results are more accurately summarised as follows. Maternal effects NOAEL 1000 mg/kg bw/day [based on the main phase and standard endpoints i.e., excluding measurement of liver enzymes and histopathology otherwise NOAEL 100 mg/kg bw/day based on adaptive findings in liver.] Developmental effects NOAEL 1000 mg/kg bw/day

Reproductive toxicity			
No.	<u>Column 1</u> Reference to CLH report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations
			[↑ fetal incidence cleft palate, no increase in litter incidence, 1 fetus also with exencephaly (1 fetus with cleft palate and exencephaly in the control group), 2 fetuses/2 litters with malposition of hindlimb (single occurrence in all other groups. Neither the type nor incidence of malformation are clearly treatment related. The malformations observed are related to the high rate of spontaneous malformation in the NMRI mouse. [See comment 29].
(34)	8.10.5 Short summary and overall relevance of the provided information on adverse effects on development	Tebuconazole Task Force: Based on our comments above, the Dossier Submitter is kindly requested to reevaluate the summary on adverse effects on development. The Task force does not agree with the current assessment.	<p>Study overview by species</p> <p>Rat: The developmental neurotoxicity study (B.6.6.2.1.2/01) demonstrated markedly reduced maternal body weight gain and food consumption from gestation day 6 to 21 at 1000 ppm (65/125 mg/kg bw/day gestation/lactation). On day 21, the mean body weight was lower than controls by 24%. A likely consequence of this was a small perturbation in the duration of gestation, a reduced number of live born and an increased number of still born offspring (although the total number was small – 7 pups from a total of 5 litters). Also, maternal body weight gain during the first week of lactation was lower than controls by 82%, followed by a 68% increase in weight gain lactation days 7 to 12. Offspring weights at birth were marginally yet not statistically significantly lower compared with controls but a clear difference was established by lactation day 5. The delay in the time of vaginal opening was considered a consequence of the lower body weight.</p> <p>The non-guideline developmental neurotoxicity study (B.6.6.2.1.2/02) demonstrated reduced maternal body weight gain 60 mg/kg bw/day. Pup viability and body weight were decreased at birth. No effect on landmarks of development or sexual maturation in the offspring.</p> <p>The conclusions from two standard developmental toxicity studies by the oral (gavage) route, are that dose levels of ≥ 60 mg/kg bw/day induced maternal toxicity. The maternal NOAEL is 30 mg/kg bw/day. Dose levels of ≥ 100 mg/kg bw/day impaired fetal viability and growth in utero</p>

Reproductive toxicity			
No.	<u>Column 1</u> Reference to CLH report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations
			<p>resulting in a small number of minor visceral / skeletal anomalies considered secondary to the severity of the maternal toxicity induced defined by initial and prolonged weight loss impacting overall weight gain. There was no clear evidence for an association with tebuconazole and fetal malformation. The external findings in the two malformed fetuses in the 120 mg/kg bw/day group were within the historical control range (fetal and litter incidences), were dissimilar in type and location and therefore indicated to be spontaneous in origin.</p> <p>Interstudy comparison of external fetal malformation in the rat (% fetuses (% litters) affected)</p>

Parameter	Tebuconazole [mg/kg bw/day]				
	0	0	60	100	120
Number of fetuses (litters) evaluated	173 (22)	288 (24)	256 (22)	174 (24)	232 (24)
Number of fetuses (litters) with findings	3 (3)	0 (0)	0 (0)	12 (9)	2 (2)
Eye	small (microphthalmia)	0.6 (4.6)	-	4.0 (25.0)	-
	absent (anophthalmia) ¹⁾	-	-	0.6 ¹⁾ (4.2)	-
Agnathia (lower jaw), microstomia, anophthalmia	-	-	-	-	0.4 (4.2)
Missing tail (agenesis)	-	-	-	-	0.4 (4.2)
Multiple malformations ²⁾	-	-	-	2.3 ²⁾ (16.7)	-

Data for the acceptable study (B.6.6.2.1.1/02) are highlighted grey and shown in bold and data for the supplementary study (B.6.6.2.1.1/01) are not.
 Data for 30 mg/kg bw/day are not shown as the purpose is to compare the malformations at higher doses

¹⁾ One foetus affected plus two with other malformations
²⁾ Two fetuses affected. One with narrow orbit; exencephaly, spina bifida, S-shaped spinal column, macroglossia, etc. One with dysplasia of scapula and long bones; encephalomeningocele, macroglossia, hydronephrosis. Both with anophthalmia.

The visceral anomalies in the 120 mg/kg bw/day group of excess fluid in the thoracic cavity observed in 4 fetuses (3.5% fetuses/8.3% litters) with no occurrence in the concurrent control group or in the historical control data. The significance of this minor anomaly is uncertain but it is considered a possible consequence of the 11% reduction in fetal body weight.

Reproductive toxicity			
No.	<u>Column 1</u> Reference to CLH report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations
			<p>The slightly elevated incidence of short supernumerary ribs (within the historical control range) in the 120 mg/kg bw/day group is a commonly occurring consequence of reduced fetal body weight in the rat, having no detrimental impact on development.</p> <p>Additionally, the incidence of fetuses with non-ossified cervical vertebrae 1-6, sacral vertebral arches 6 and 7, various phalangeal nuclei and incompletely ossified sternebra 2 were increased in the 120 mg/kg bw/day group, and significantly different from the control value, providing further evidence of retarded ossification due to lower body weight as a consequence of maternal toxicity. Therefore, the developmental NOAEL is 60 mg/kg bw/day.</p> <p>There are no relevant observations from the published studies worthy of consideration that alter this conclusion.</p> <p>Rabbit: Three prenatal developmental toxicity studies have been conducted in the rabbit (Himalayan & Chinchilla) using the oral gavage route of administration. Two studies using the Chinchilla rabbit are considered acceptable. The severity of maternal toxicity due to 100 mg/kg bw/day impacted fetal growth (lower fetal body weight) and fetal viability (increased post-implantation loss). The NOAEL was 30 mg/kg bw/day. Neither the type nor incidence of malformation were reproducible across studies or consistent with dose in the same strain of rabbit. No malformation was noted in the Himalayan rabbit study providing supplementary data. The historical data for the Chinchilla rabbit demonstrate a peak in malformation at the time of one study. The developmental NOAEL was 30 mg/kg/day.</p>

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			<p>Interstudy comparison of external fetal malformation in the Chinchilla rabbit (% fetuses (% litters) affected)</p> <table border="1"> <thead> <tr> <th rowspan="2">Parameter</th> <th colspan="6">Tebuconazole [mg/kg bw/day]</th> </tr> <tr> <th>0</th> <th>0</th> <th>30</th> <th>30</th> <th>100</th> <th>100</th> </tr> </thead> <tbody> <tr> <td>Number of fetuses (litters) evaluated</td> <td>111 (15)</td> <td>141 (16)</td> <td>122 (15)</td> <td>109 (14)</td> <td>90 (14)</td> <td>119 (14)</td> </tr> <tr> <td>Number of fetuses (litters) with findings</td> <td>0 (0)</td> <td>0 (0)</td> <td>0 (0)</td> <td>3 (3)</td> <td>8^a (5)</td> <td>3 (3)</td> </tr> <tr> <td>Multiple malformations</td> <td>-</td> <td>-</td> <td>-</td> <td>0.9^b (7.1)</td> <td>-</td> <td>2.5^c (21.4)</td> </tr> <tr> <td>Hindlimb malrotated (also hydrocephalus internus)</td> <td>-</td> <td>-</td> <td>-</td> <td>-</td> <td>1.1 (6.7)</td> <td>-</td> </tr> <tr> <td>Hindlimb malrotated, pes varus position, brachydactyly, missing phalanges</td> <td>-</td> <td>-</td> <td>-</td> <td>0.9 (7.1)</td> <td>-</td> <td>-</td> </tr> <tr> <td>Hindlimb hyperflexion (Arthrogryposis without skeletal finding)</td> <td>-</td> <td>-</td> <td>-</td> <td>0.9 (7.1)</td> <td>-</td> <td>-</td> </tr> <tr> <td>Hemimelia (peromelia)^d</td> <td>-</td> <td>-</td> <td>-</td> <td>-</td> <td>5.6 (26.7)</td> <td>-</td> </tr> <tr> <td>Claw absent (agenesis)</td> <td>-</td> <td>-</td> <td>-</td> <td>-</td> <td>1.1 (6.7)</td> <td>-</td> </tr> <tr> <td>Cleft palate (palatoschisis)</td> <td>-</td> <td>-</td> <td>-</td> <td>-</td> <td>1.1 (6.7)</td> <td>-</td> </tr> </tbody> </table> <p>^a Skeletal anomalies occurred in 6 of these fetuses ^b Craniochisis, dysplastic skull, protruding tongue, kyphosis, spina bifida aperta, eventration of organs, open eye, shorter extremities, bent forepaw, brachydactyly ^c Meningocele or partial acephaly, omphalocele or abdominal fissure, spina bifida occipitale (2 fetuses), malposition of limb brachydactyly, shortened tail (1 fetus) ^d Doubts were raised about the accuracy of the finding peromelia No highlight or bold font denotes study B.6.6.2.2.1/02. Grey highlight and bold font denotes study B.6.6.2.2.1/03. Data for 10 mg/kg bw/day not shown as purpose is to show higher dose incidence malformation</p> <p>Mouse: Maternal toxicity due to 100 mg/kg bw/day impacted fetal growth (lower fetal body weight) and fetal viability (increased post-implantation loss). The maternal NOAEL was 10 mg/kg bw/day based on changes observed in the liver, and not body weight. The developmental NOAEL was 30 mg/kg bw/day.</p>	Parameter	Tebuconazole [mg/kg bw/day]						0	0	30	30	100	100	Number of fetuses (litters) evaluated	111 (15)	141 (16)	122 (15)	109 (14)	90 (14)	119 (14)	Number of fetuses (litters) with findings	0 (0)	0 (0)	0 (0)	3 (3)	8 ^a (5)	3 (3)	Multiple malformations	-	-	-	0.9^b (7.1)	-	2.5^c (21.4)	Hindlimb malrotated (also hydrocephalus internus)	-	-	-	-	1.1 (6.7)	-	Hindlimb malrotated, pes varus position, brachydactyly, missing phalanges	-	-	-	0.9 (7.1)	-	-	Hindlimb hyperflexion (Arthrogryposis without skeletal finding)	-	-	-	0.9 (7.1)	-	-	Hemimelia (peromelia) ^d	-	-	-	-	5.6 (26.7)	-	Claw absent (agenesis)	-	-	-	-	1.1 (6.7)	-	Cleft palate (palatoschisis)	-	-	-	-	1.1 (6.7)	-
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¹ B.6.6.2.3.1/01 ² B.6.6.2.3.1/03 ³ B.6.6.2.3.2/01
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(35)	Data overview development page 80 maternal effects	<p>Tebuconazole Task Force: It is reported that observed developmental effects were in some but not all cases associated with statistically significant maternal effects on body weight gains, liver and adrenal changes.</p> <p>The effects on 1) post-implantation loss and perinatal death, 2) fetal/pup growth impairment, and 3) external malformations including cleft palates are not adequately summarised. The developmental effects (1) and (2) do occur in the presence of decreased maternal body weight gain during gestation and /or lactation as shown in the tables in column 3.</p> <p>The open literature studies are unreliable and should not contribute to this overall assessment.</p> <p>The speculation that fetal death could be attributed to lower total litter weights is not supported. Such an opinion needs to be substantiated by statistical analysis using litter size as a covariant.</p> <p>The dossier submitter is kindly requested to reevaluate the appraisal by species and dose based on reliable study data.</p>	<table border="1"> <thead> <tr> <th>Study Type</th> <th>Reference</th> <th></th> <th>High dose (mg/kg/day)</th> <th>Maternal weight gain gestation ↓</th> <th>Observation: post-implantation loss / fetal death</th> </tr> </thead> <tbody> <tr> <td>2 GEN diet</td> <td>B.6.6.1.1/01</td> <td>F0a</td> <td>94</td> <td>-16%</td> <td>↓ litter size at birth -15%</td> </tr> <tr> <td>2 GEN diet</td> <td>B.6.6.1.1/01</td> <td>F0b</td> <td>94</td> <td>-14%</td> <td>↓ litter size at birth -26%</td> </tr> <tr> <td>2 GEN diet</td> <td>B.6.6.1.1/01</td> <td>F1a</td> <td>111</td> <td>-6%</td> <td>no effect</td> </tr> <tr> <td>2 GEN diet</td> <td>B.6.6.1.1/01</td> <td>F1b</td> <td>111</td> <td>-8%</td> <td>no effect</td> </tr> <tr> <td>DNT GLP diet</td> <td>B.6.6.2.1.2/01</td> 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dose (mg/kg/day)	Maternal weight gain gestation ↓	Observation: post-implantation loss / fetal death	2 GEN diet	B.6.6.1.1/01	F0a	94	-16%	↓ litter size at birth -15%	2 GEN diet	B.6.6.1.1/01	F0b	94	-14%	↓ litter size at birth -26%	2 GEN diet	B.6.6.1.1/01	F1a	111	-6%	no effect	2 GEN diet	B.6.6.1.1/01	F1b	111	-8%	no effect	DNT GLP diet	B.6.6.2.1.2/01		65	-22%	↓ mean number live born (13.1 cf. 13.9 controls), ↑ still born (7 cf. 2 controls), ↑ neonatal deaths (22 cf. 4 controls), ↓ viability index LD5 (91.7% cf. 97.9% controls)	DNT NON GLP Oral Publication	B.6.6.2.1.2/02		60	-16%	↓ number live pups (9.7 cf. 11.2 controls), ↑ number dead pups (2.2 cf. 0.4 controls)	Rat PND Oral	B.6.6.2.1.1/01		100	-74%	post-implantation loss not reported, no clear effect on fetal death (↑ late resorptions (2.3 cf. 1.4 controls) but no ↓ in number live fetuses (7.3 cf. 7.9 control)	Rat PND Oral	B.6.6.2.1.1/02		120	-29%	↑ post-implantation loss (22.1% cf. 4.6% controls) hence ↓ number live fetuses (9.7 cf. 12.0 controls)	Rat PND Oral Maternal Tox	B.6.6.2.1.1/03		120	-60%	↑ post-implantation loss (21.8% cf. 6.0% controls) hence ↓ number live fetuses (9.5 cf. 11.1 controls)	Rat PND Dermal	B.6.6.2.1.3/01		1000	no effect	no effect	Rat PND Dermal	B.6.6.2.1.3/02		1000	no effect	no effect	Rabbit PND Oral	B.6.6.2.2.1/01		30	-26%	non-significant ↑ post-implantation loss with no corresponding ↓ number live fetuses	Rabbit PND Oral	B.6.6.2.2.1/02		100	-38%	↑ post-implantation loss 27.4% cf. 8.3% controls, hence ↓ number live fetuses (6.4 cf. 7.4 controls)	Rabbit PND Oral	B.6.6.2.2.1/03		100	-59%	marginal, non-significant ↑ post-implantation loss with no ↓ number live fetuses	Rabbit PND Oral Mechanistic	B.6.6.2.2.1/04		100	(-181%)	no effect but termination on GD19 (ahead of the period of fetal growth)	Mouse PND Oral	B.6.6.2.3.1/01		100	no effect	post-implantation loss not reported, no effect on litter size	Mouse PND Oral Maternal Tox	B.6.6.2.3.1/02		100	-32%	unreliable data (small sample size, low pregnancy rate, inconsistent dose response)	Mouse PND Oral	B.6.6.2.3.1/03		100	-13%	↑ post-implantation loss (35.3% cf. 8.4% controls) hence ↓ number live fetuses (8.1 cf. 10.9 controls)	Mouse PND Dermal	B.6.6.2.3.2/01		1000	no effect	no effect	Publication	B.6.6.3/04		50		unreliable data (small number of animals, inconsistent results etc.)	Publication	B.6.6.3/05		50		unreliable data (small number of animals, inconsistent results etc.)	Publication	B.6.6.3/06		50		unreliable data (small number of animals, inconsistent results etc.)	Publication	B.6.6.3/07		100		unreliable data (small number of animals, inappropriate data handling, highly variable and inconsistent results etc.)	Publication	B.6.6.3/08		50		unreliable data (small number of animals, highly variable results etc.)	Pubertal	B.6.8.3.1.2/01		150		no relevant data	Pubertal Publication	B.6.8.3.1.2/02		100		no relevant data
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Rat PND Oral	B.6.6.2.1.1/02		120	-29%		↓ fetal body weight (-11%)																																																																																																																																																																																												
Rat PND Oral Maternal Tox	B.6.6.2.1.1/03		120	-60%		↓ fetal body weight (-13%)																																																																																																																																																																																												
Rat PND Dermal	B.6.6.2.1.3/01		1000	no effect		no effect																																																																																																																																																																																												
Rat PND Dermal	B.6.6.2.1.3/02		1000	no effect		no effect																																																																																																																																																																																												
Rabbit PND Oral	B.6.6.2.2.1/01		30	-26%		no effect																																																																																																																																																																																												
Rabbit PND Oral	B.6.6.2.2.1/02		100	-38%		↓ fetal body weight (-6%)																																																																																																																																																																																												
Rabbit PND Oral	B.6.6.2.2.1/03		100	-59%		↓ fetal body weight (-7%)																																																																																																																																																																																												
Rabbit PND Oral Mechanistic	B.6.6.2.2.1/04		100	(-181%)		↓ fetal body weight (-12% GD 19)																																																																																																																																																																																												
Mouse PND Oral	B.6.6.2.3.1/01		100	no effect		no effect																																																																																																																																																																																												
Mouse PND Oral Maternal Tox	B.6.6.2.3.1/02		100	-32%		no data																																																																																																																																																																																												
Mouse PND Oral	B.6.6.2.3.1/03		100	-13%		↓ fetal body weight (-8%)																																																																																																																																																																																												
Mouse PND Dermal	B.6.6.2.3.2/01		1000	no effect		no effect																																																																																																																																																																																												
Publication	B.6.6.3/04		50			unreliable data (small number of animals, inconsistent results etc.)																																																																																																																																																																																												
Publication	B.6.6.3/05		50			unreliable data (small number of animals, inconsistent results etc.)																																																																																																																																																																																												
Publication	B.6.6.3/06		50			unreliable data (small number of animals, inconsistent results etc.)																																																																																																																																																																																												
Publication	B.6.6.3/07		100			unreliable data (small number of animals, inappropriate data handling, highly variable and inconsistent results etc.)																																																																																																																																																																																												
Publication	B.6.6.3/08		50			unreliable data (small number of animals, highly variable results etc.)																																																																																																																																																																																												
Pubertal	B.6.8.3.1.2/01		150			no relevant data																																																																																																																																																																																												
Pubertal Publication	B.6.8.3.1.2/02		100			no relevant data																																																																																																																																																																																												
(36)	Data overview development page 80 External malformations	Tebuconazole Task Force: The association with tebuconazole and malformation appears to be based on an assumption that all malformations observed are chemically induced. If the data are considered carefully by species, by dose and by reproducibility it is clear that there is no evidence for an effect of the chemical. The dossier submitter is kindly requested to reevaluate their appraisal.	See responses in (29), (31) and (32) above. The mouse strain is clearly unsuitable for use as demonstrated by the control incidence of malformation.																																																																																																																																																																																															
(37)	8.10.3 Page 60 Mode of action analysis	Tebuconazole Task Force: we disagree with the postulated mode of action showing a relationship between disruptions in steroidogenesis (MIE), reduced serum estradiol levels (KE1) and the	Increased post-implantation loss (late resorptions in rats, early resorptions in rabbits and mice), postnatal death and retarded fetal development of pups were in most cases limited to high dose exposure (≥ 65 mg/kg bw/day) and always associated with clear maternal toxicity. Similarly,																																																																																																																																																																																															

Reproductive toxicity			
No.	<u>Column 1</u> Reference to CLH report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations
	AO: Post-implantation loss- (including fetal deaths and decreased litter size) KE1: reduced serum estradiol	adverse outcome: "post-implantation loss (including fetal deaths and decreased litter size)". Please see further explanations regarding post implantation loss in column 3 Moreover, the postulated mode of action analysis is flawed based on a lack of evidence for disrupted steroidogenesis and reduced estradiol due to tebuconazole. Please see also comment (11a) regarding the KE1 "reduced serum estradiol"	fetal/pup weight and pup weight development were only decreased at ≥ 60 mg/kg bw/day. The only exemption is the unreliable rat study (B.6.6.3/08; klimisch 3) in which tebuconazole induced a high frequency (11.4% vs. 0% in the control group) of post-implantation loss at 50 mg/kg bw/day. In another unreliable Klimisch 3 study from the same author (B.6.6.3/07), no significant toxic effects on rat fetuses with a dose of 50 mg/kg bw/day were reported. The latter result is supported by two further publications from the same test facility (B.6.6.3/07; B.6.6.3/05) also considered Klimisch 3 in which the number of implantation scars in the uterus, post-implantation and perinatal loss was also similar among treatment and control groups up to and including the highest tested dose of 50 mg/kg bw/day. Please see also comment (35) regarding the data overview-development/ Maternal effects
(38)	Conclusion in relation to CLP criteria – development	Tebuconazole Task Force: we disagree that classification of tebuconazole for developmental toxicity in category 1B (Repr. 1B; H360D) is warranted. The dossier submitter is kindly requested to consider our comments before reaching their conclusion.	
(39)	8.10.7 Lactation Table 57 B.6.6.2.1.1/01 & B.6.6.2.1.1/02	Tebuconazole Task Force: Table states, please refer to table 46. Table 46 is Compilation of factors to be taken into consideration in the hazard assessment for tumours. Error needs correction.	

Neurotoxicity			
No.	<u>Column 1</u> Reference to CLH report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations
(1)	<<data point>>, <<description>>	<<MS/EFSA/applicant>>: <<comment>>	

Further toxicological studies			
No.	<u>Column 1</u> Reference to CLH report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations

Toxicological data on metabolites			
No.	<u>Column 1</u> Reference to CLH report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations
(1)	<<data point>>, <<description>>	<<MS/EFSA/applicant>>: <<comment>>	

Medical data and information			
No.	<u>Column 1</u> Reference to CLH report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations
(1)	<<data point>>, <<description>>	<<MS/EFSA/applicant>>: <<comment>>	

Other comments, proposals for classification			
No.	<u>Column 1</u> Reference to CLH report	<u>Column 2</u> Comment (restricted to 500 characters, ca.10 lines)	<u>Column 3</u> Further explanations
(1)	<<data point>>, <<description>>	<<MS/EFSA/applicant>>: <<comment>>	